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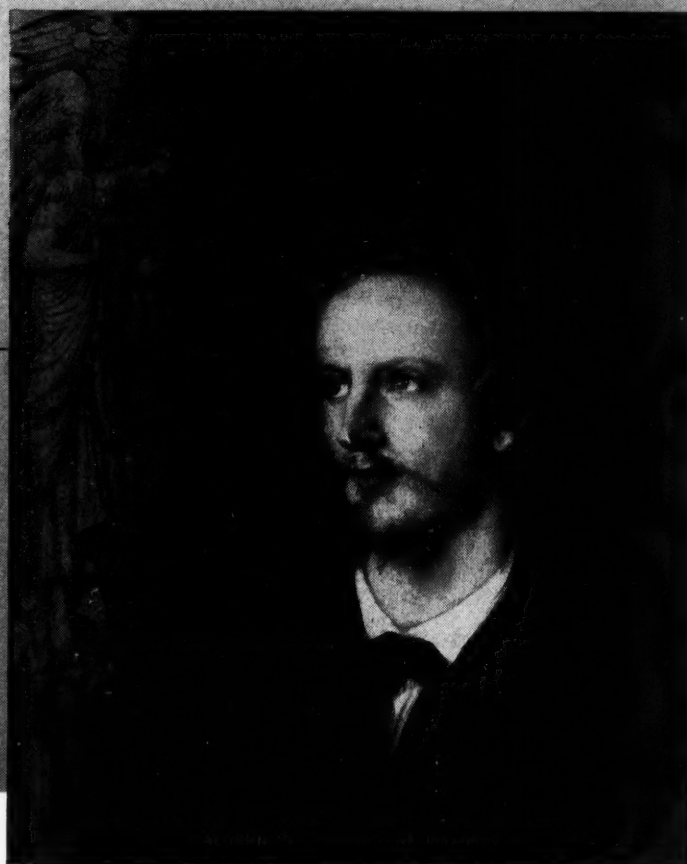
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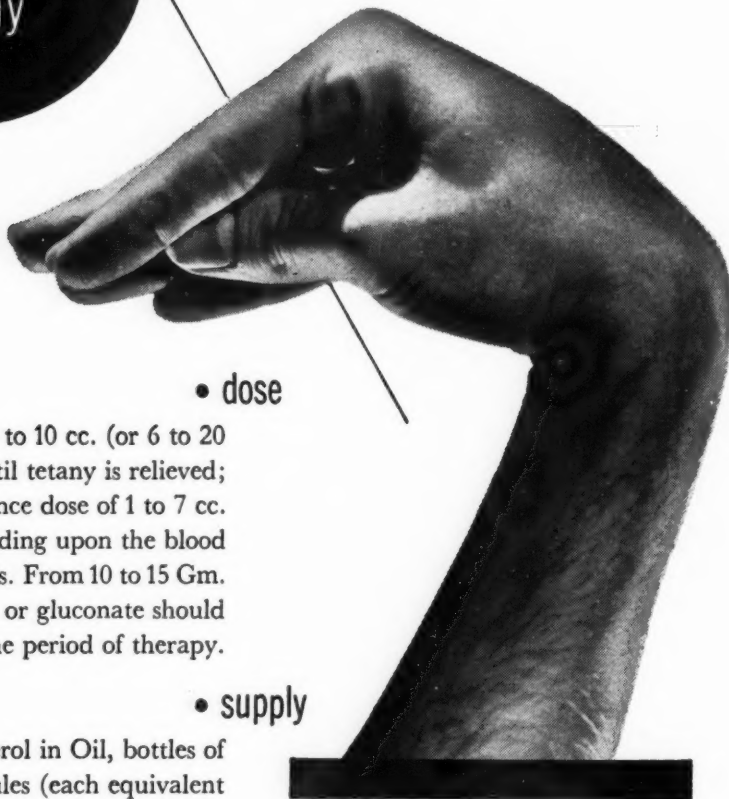
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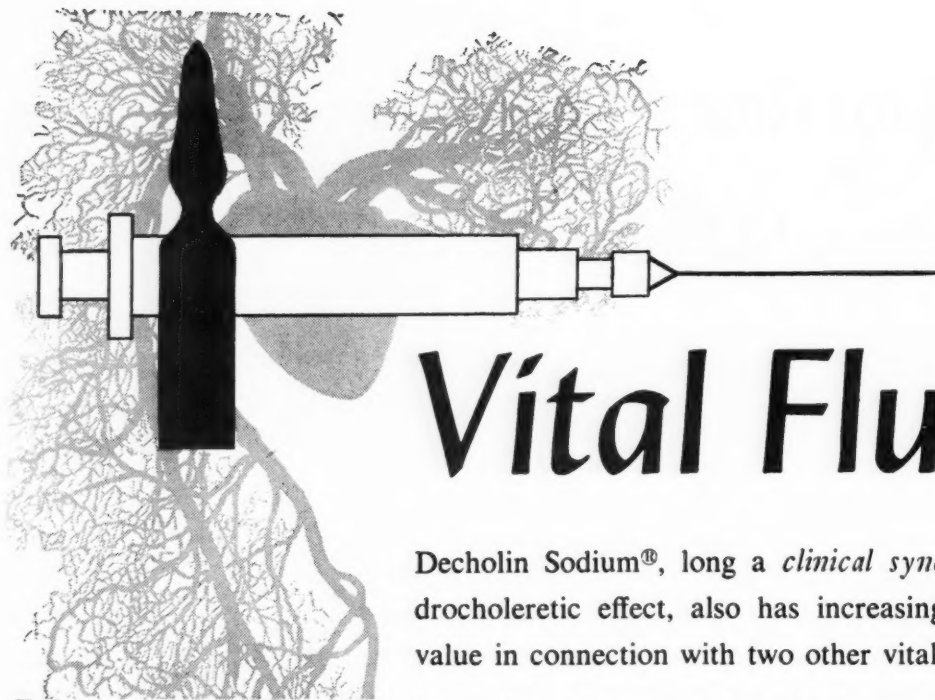
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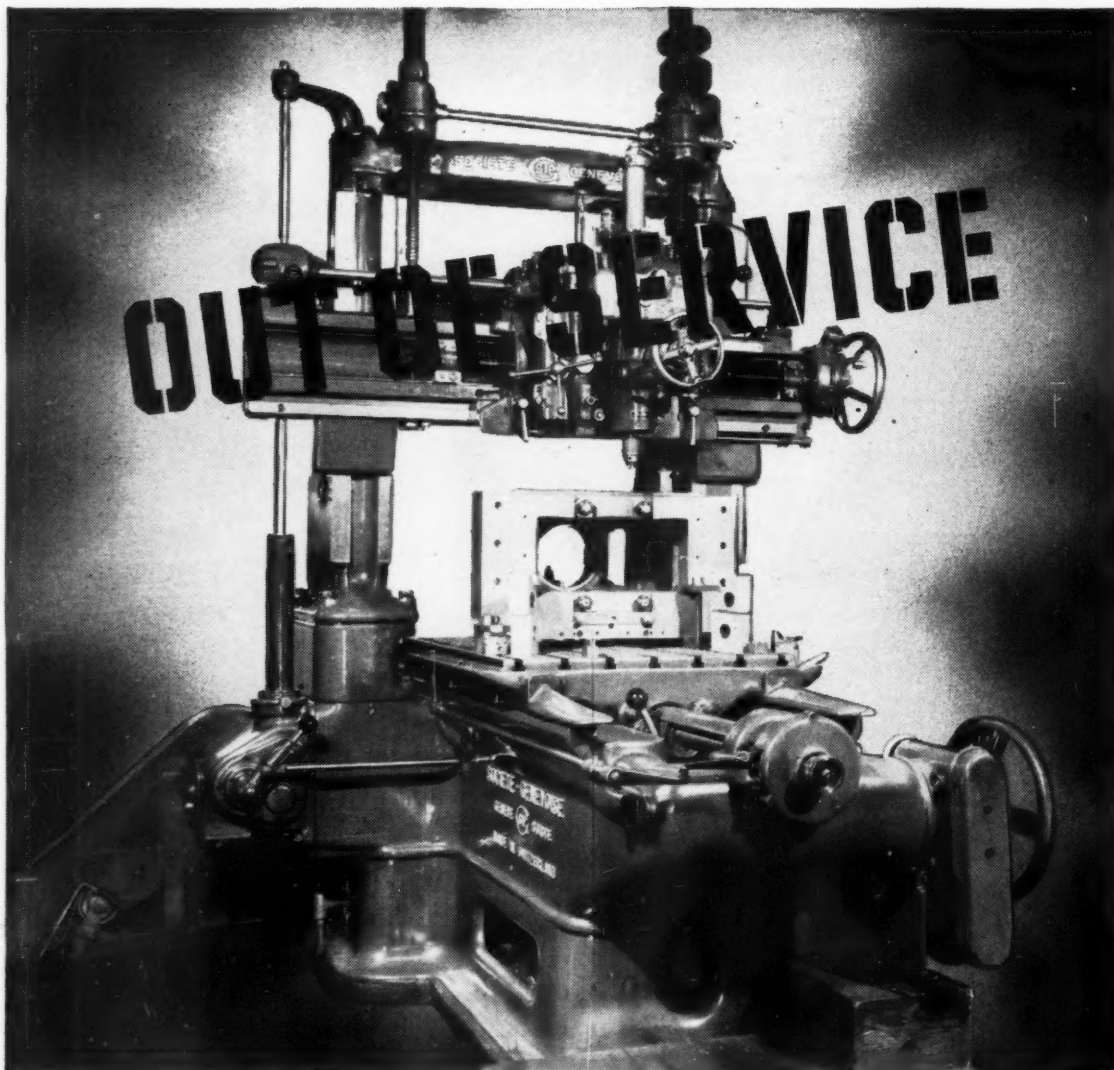
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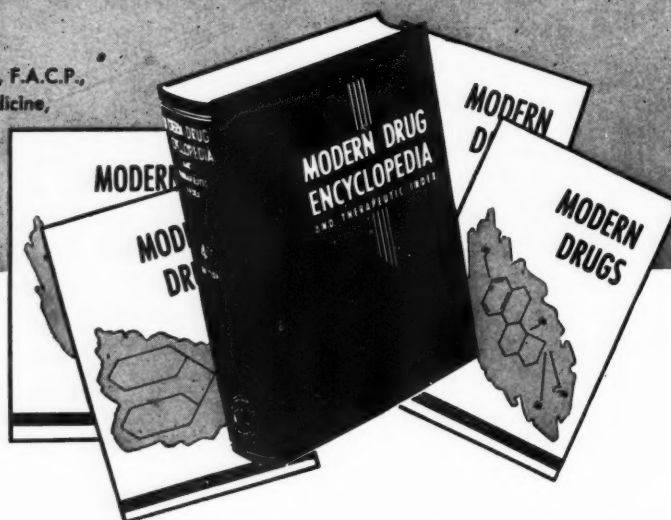
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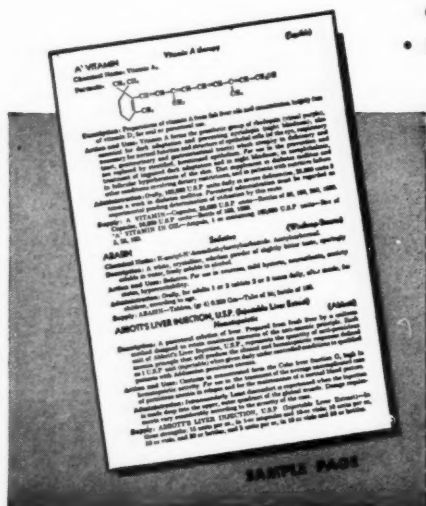
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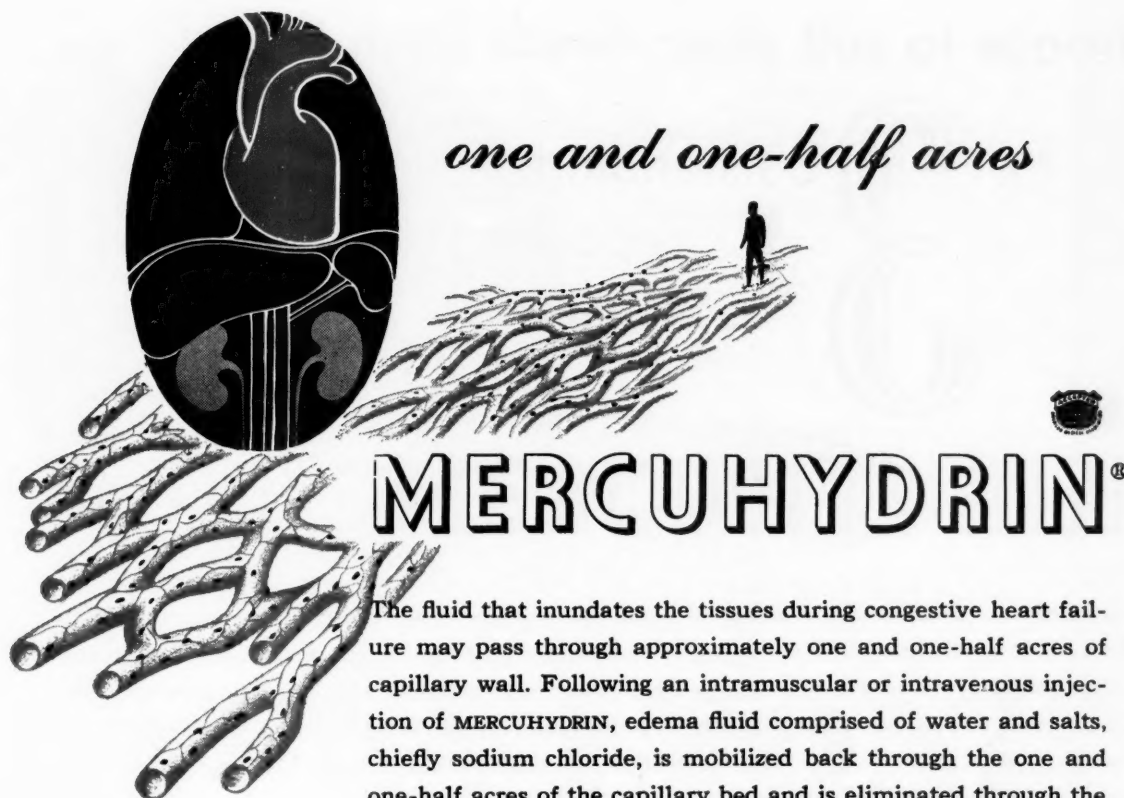
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*Fishberg, A. M.: Heart Failure, Lea and Febiger, Philadelphia, 1946, p. 733.

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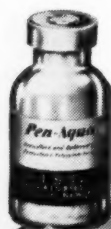
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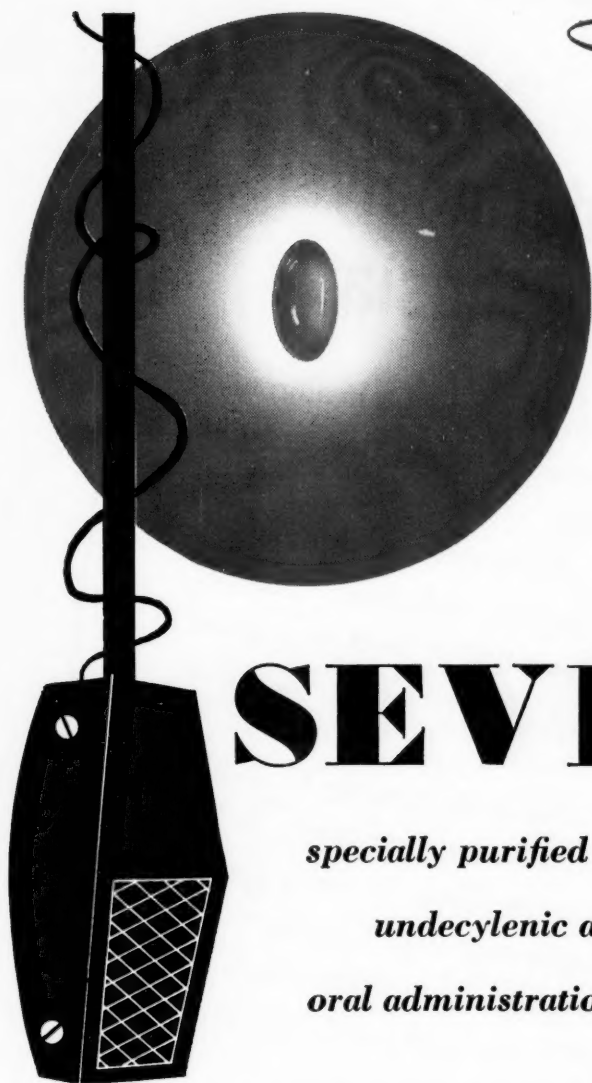


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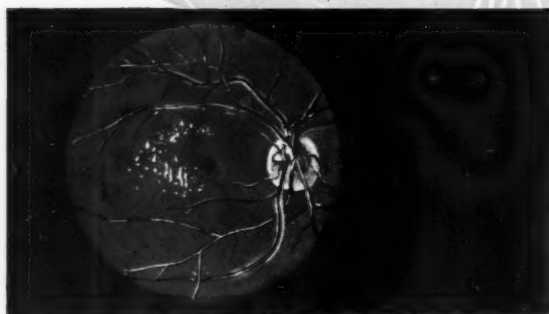
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1. Freis, E. D.: Med. Clin. N. Am. 32:1247-1258, 1948.

2. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36:723-738, 1948.

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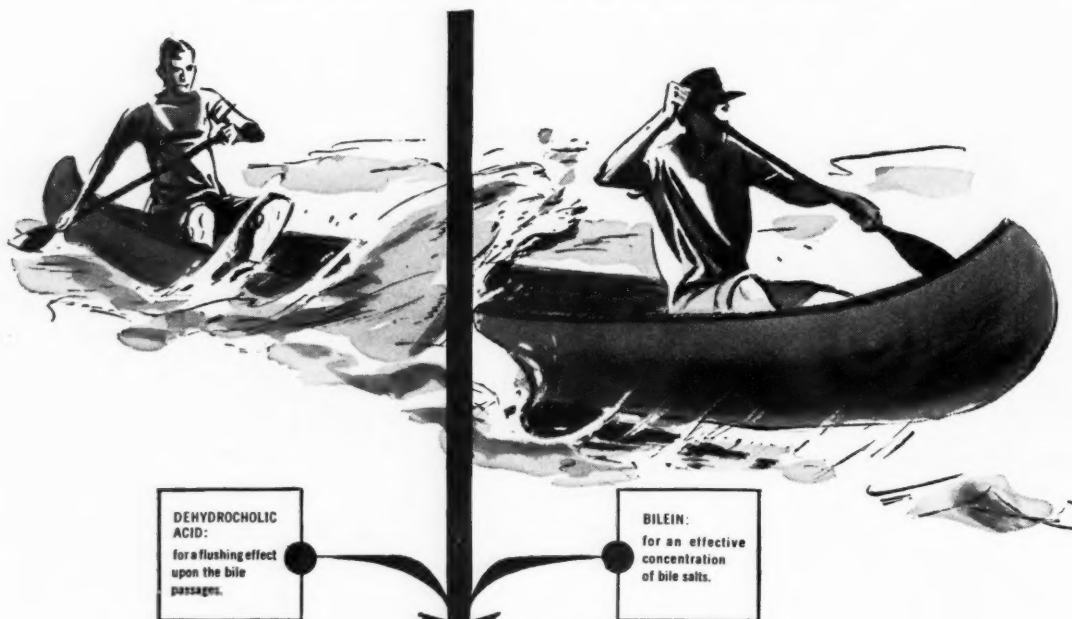
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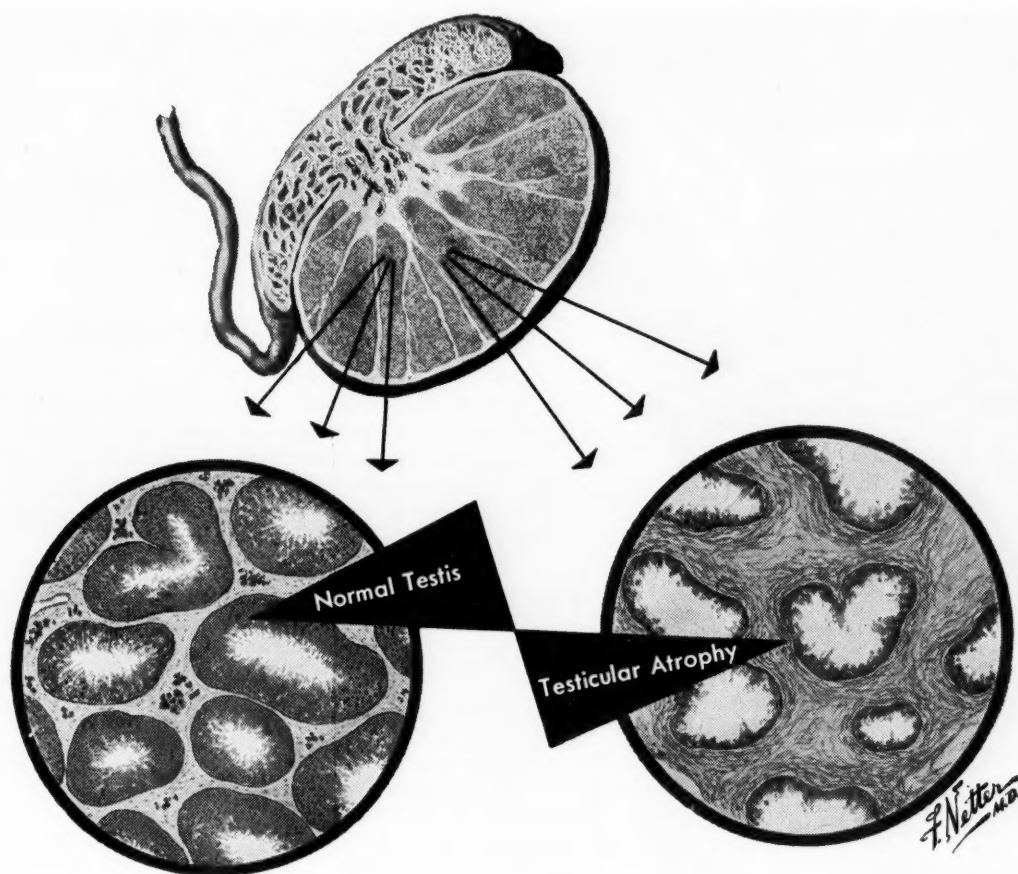
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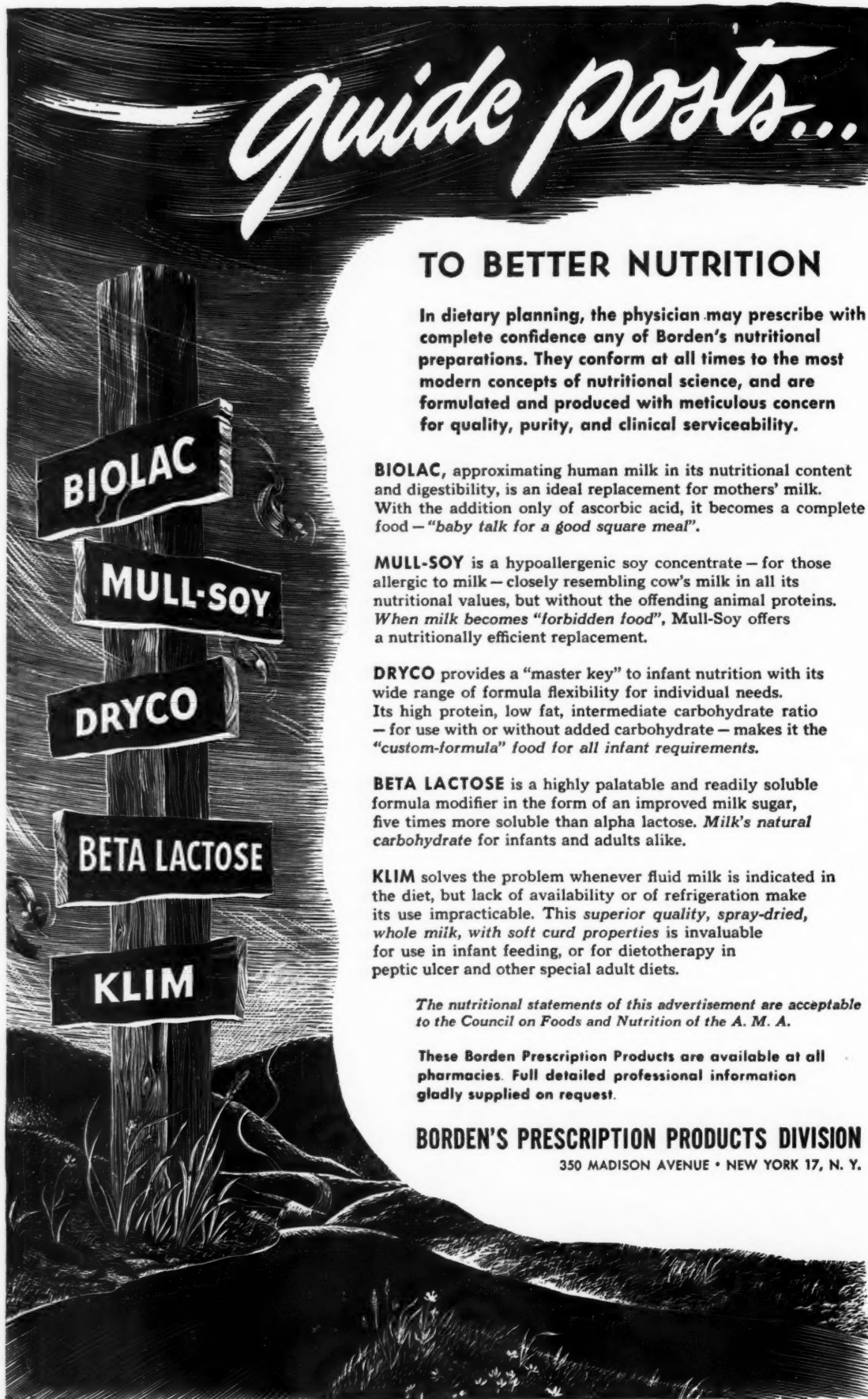
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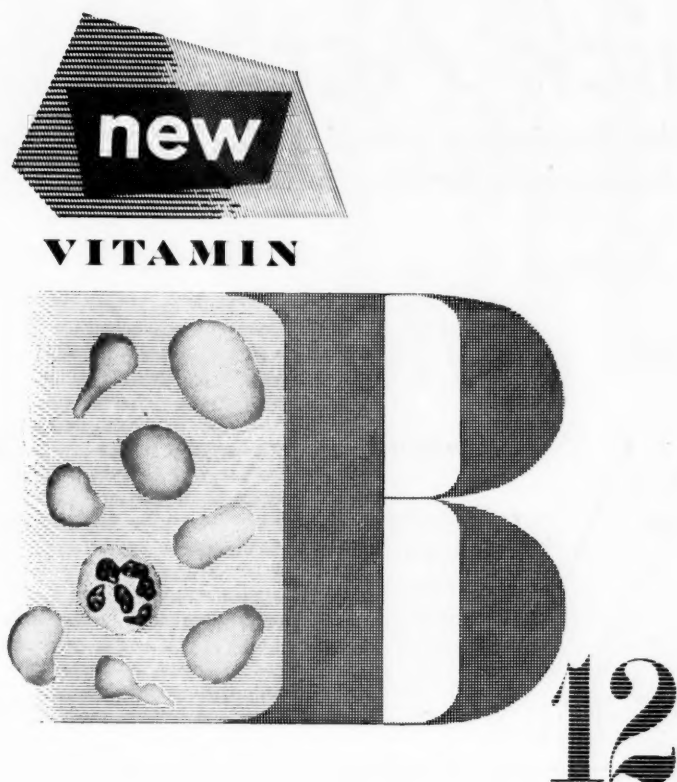
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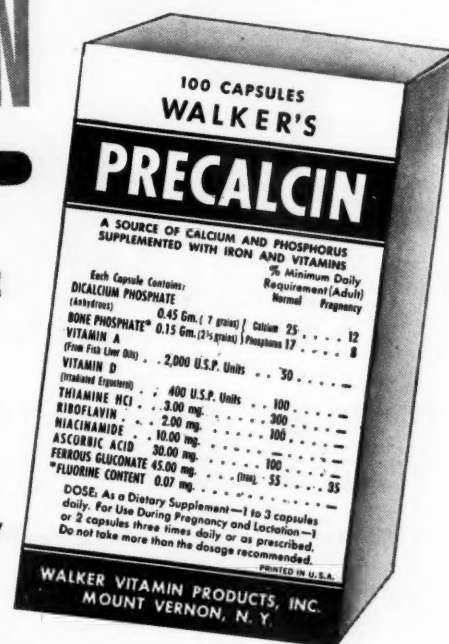
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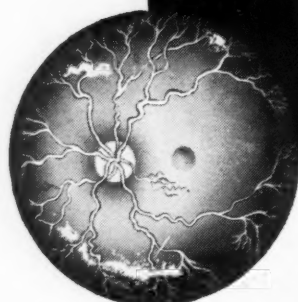
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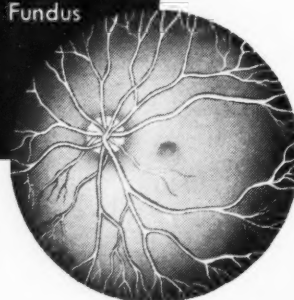
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1. Carroll, G., and Allen, N. H.: J. Urol. 55: 674 (1946).

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The American Journal of Medicine

Vol. VII

JULY, 1949

No. 1

Editorial

Retrospect and Prospect, 1949

THE American Journal of Medicine with this issue initiates its fourth year of publication. The editor takes the occasion to report upon the progress and problems of the past year, and the plans for the forthcoming twelve months.

Friends of the Journal will be pleased to know that The American Journal of Medicine in the past year continued its steady growth and, indeed, appears already to have attained the largest circulation in its class of "independent" medical journals (i.e., journals not serving as official organs of medical societies) which are published monthly. This is an unexpected accomplishment, particularly within so short a time as three years.

Gratifying as is such growth, the really significant fact is that this popularity has been achieved without deviation from the avowed policy of the Journal to maintain the highest standards in publication of clinical research and in the presentation of advanced teaching programs from leading medical schools and hospital clinics. We have made no compromises whatever in this regard and, indeed, there is every indication that The American Journal of Medicine has found favor because it aims high. The rapid growth of the Journal would seem fully to vindicate this stringent policy and to demonstrate that there are real needs at this level which the Journal is helping to meet.

A feature of the Journal which has attracted widespread interest are the symposia, two of which appear each year. Their organization is delegated to some authority in the

field selected, who serves as guest editor, and they are planned with great care to stimulate as well as to inform. The subject matter usually deals with a discipline which should not be but often is divorced from the narrow channels of internal medicine, to the disadvantage both of the internist and the specialty discipline. Two exceptionally fine symposia of this kind appeared in The American Journal of Medicine in the past year, one on syphilis, the other on poliomyelitis; both especially designed for the needs of a general medical audience and from all accounts serving a most useful purpose. During the coming year symposia on diabetes and on infectious hepatitis have been scheduled and they are expected to maintain the high standards established by their predecessors.

The seminars are invited papers presenting different points of view on large and usually controversial issues of current interest, the final paper being assigned with the view of attempting to integrate the arguments previously presented. These articles appear in six consecutive issues of the Journal, one topic being covered every six months. During the past year two lively and illuminating series of seminars brought together the work and concepts of leaders in the fields of protein hydrolysates and of mechanisms of congestive failure, both series helping much to clarify thinking in these difficult subjects. The next series will deal with the newer antibiotics, the first contribution, by Dr. Waksman, appearing in this issue.

Each issue of the Journal also contains a review article on some topic of current interest. In the selection of these reviews preference has been given to those that assimilate rather than recite published data, presenting critically integrated and constructive points of view which may be more original than some so-called original reports and certainly more helpful in advancing knowledge and understanding; indeed, many of these reviews contain an abundance of new facts and ideas. Opportunity is afforded also for reasoned speculation and broad philosophic discussion for which a suitable outlet is so much needed.

The various Conferences remain the keystone of the teaching effort of the Journal. These combined staff conferences represent a peculiarly American contribution to medical pedagogy, a replacement of the star system, limited to a solitary presentation, by the team system coordinating the efforts of those with special interests and experience. The team approach brings to bear upon medical problems a fullness which one man alone can rarely approach and has the collateral advantage of providing common ground for different disciplines which otherwise tend to go their several ways to the detriment of progress both in medicine and in the basic sciences. Throughout the coming year The American Journal of Medicine will continue publication of the Cornell Conferences on Therapy, the Columbia Combined Staff Clinics, the Washington University Clinicopathologic Conferences and the Harvard Conferences on Psychosomatic Problems. Each of these conferences comes directly from the classrooms of the respective university hospitals represented; all are painstakingly planned and edited to make effective teaching exercises of sustained interest. It is hoped in this way to continue to exploit the opportunities presented by the Journal to extend facilities for instruction at a high postgraduate level.

An important function of The American Journal of Medicine is to publish the results of original clinical investigation. Here we have sought a middle ground between

highly specialized research of immediate interest to very few and repetitious accounts of clinical experiences already familiar to most. The chief difficulty of the editor in this regard has been to limit the acceptance of studies of the desired character and scope to the number that could be published within a reasonable time. The flow of fine papers from all parts of the country has been so heavy that it has, unfortunately, been necessary to turn away many meritorious studies simply because of limitations in space. Moreover, in order to ensure current interest it has been necessary to disregard the chronologic order of receipt of manuscripts and give precedence to those urgent communications which would suffer most by delay. These efforts have kept the Journal up-to-date and have resulted in a net shortening of the publication period but there is still a large backlog of manuscripts. Every effort is being made to expedite the publication of these articles.

In addition to formal presentations of the results of clinical research the Journal publishes in abstract form the scientific proceedings of various sections of the American Federation for Clinical Research, the Western Society for Clinical Research and the Southern Society for Clinical Research. These proceedings describe a wide variety of research activities and are of unusual interest. It is planned to continue their publication throughout the next year.

In concluding, the editor wishes to take this opportunity to express his indebtedness to the many who have contributed so generously of their time and energy to strengthen the effectiveness of the Journal in its various programs. Thanks are due also to the confidence and support of the growing host of friends whose interest in the Journal has ensured its success. It shall continue to be the endeavor of the publishers and the editorial board to maintain a position of respect and affection for The American Journal of Medicine among the established medical journals of the country.

ALEXANDER B. GUTMAN, M.D.

AMERICAN JOURNAL OF MEDICINE

Clinical Studies

Clinical Manifestations of Intercapillary Glomerulosclerosis in Diabetes Mellitus*

GEORGE V. MANN, M.D., CARL GARDNER, M.D. and HOWARD F. ROOT, M.D.

Boston, Massachusetts

THE fact that the presence of diabetes mellitus accelerates development of vascular sclerosis in humans has long been well established. The excessive frequency of advanced arteriosclerotic lesions commented upon by Aschoff,^{1,2} and

death in patients with diabetes emphasizes that with the availability of insulin and dissemination of the knowledge necessary for its proper use the number of deaths due to diabetic coma has steadily declined. Concomitant with this reduction in coma

TABLE I
INFLUENCE OF DURATION OF DIABETES MELLITUS UPON PERCENTAGE OF TOTAL DEATHS IN DIABETICS DUE TO ARTERIOSCLEROSIS AND TO DIABETIC COMA

	Average Duration of Diabetes (yr.)*	Deaths (total)	Coma (%)	Arterio-sclerosis (%)	Average Age at Death (yr.)
Naunyn					
1898 to June, 1914.....	4.9	326	64	17	44.5
Allen					
June, 1914 to August, 1922.....	6.1	836	42	24	46.7
Banting					
August, 1922 to December 31, 1925.....	7.5	537	21	41	54.3
January, 1926 to December 31, 1929.....	8.4	918	11	49	60.0
January, 1930 to December 31, 1934.....	10.0	1741	5	58	62.7
January, 1935 to December 31, 1936.....	11.6	793	4	59	63.9
Hagedorn					
January, 1937 to December 31, 1939.....	12.4	1229	4	62	64.8
January, 1940 to December 31, 1943.....	13.3	1354	3	66	65.0
Charles H. Best					
January, 1944 to date.....	14.1	651	3	67	64.5

* Based on cases of known duration. Deaths reported through May 15, 1946. (Adapted from JOSLIN et al., 8th ed. Treatment of Diabetes Mellitus. Philadelphia, 1946. Lea and Febiger.)

demonstrated in the first and succeeding autopsy series at the New England Deaconess Hospital, has been noted by many writers.³ The premature development in diabetic youths of arteriosclerosis with renal and retinal lesions is well known.⁴ Consideration of statistical trends of causes of

deaths and the great prolongation of the lives of diabetics an increase has developed in the percentage of diabetic deaths due to arteriosclerosis. (Table I.)

With the advent of antibiotic therapy of infectious disease, the number of diabetics who survive these acute obstacles, only to

* From The George F. Baker Clinic, New England Deaconess Hospital and The Department of Medicine, Peter Bent Brigham Hospital, Boston, Mass. This work was supported by a grant from the Life Insurance Medical Research Fund.

die of one or another of the diseases secondary to arteriosclerosis, has steadily increased. However, the possibility of postponement of premature sclerotic lesions has been demonstrated by the absence of such lesions in twenty-eight of 192 childhood diabetics who survived twenty years of diabetes.⁵

The commonest cause of death in diabetes mellitus is disease of the coronary arteries.⁶ There is no reason to believe that coronary artery disease in diabetics differs in the histopathologic sense from the disease in non-diabetics. The same applies to sclerotic disease of the cranial vessels.

Renal disease as a complication of diabetes has attracted attention first, because of its steadily increasing frequency and second, because there is some evidence, both clinical and pathologic, to indicate that there may be a type of renal disease characteristic of patients with diabetes mellitus.

Interest in nephritis as a complication of diabetes was aroused in 1936 with the description by Kimmelstiel and Wilson⁷ of unusual lesions in the renal glomeruli of a small series of patients, most of whom were known to have been diabetic. These lesions consisted of depositions of faintly acidophilic, hyalinized material in the glomerular tufts. Similar lesions have since been described many times.⁸⁻¹⁰ There is no doubt now that indistinguishable lesions may occur occasionally in non-diabetic patients, nor do all diabetic patients inevitably develop these lesions. Estimates of the incidence of these lesions in diabetic patients vary from 18 to 63 per cent in surveys of autopsy material from various hospitals. The variation in these estimates would seem to be due largely to disagreement among pathologists as to the criteria to be employed in the anatomic diagnosis.

Kimmelstiel and Wilson, on the basis of experience with eight patients, described an associated triad of clinical findings: (1) a history of diabetes mellitus, (2) edema and (3) albuminuria. It now appears that the histologic lesions when found in the kidneys are not a specific indication of diabetes;

neither is the presence of diabetes with edema, albuminuria, hypertension and renal failure evidence that the anatomic lesions will invariably be found.¹¹

The classification of renal disease in diabetics has been obscured by the tendency to group all patients into two groups, chronic glomerular nephritis and chronic pyelonephritis. Acute glomerular nephritis in diabetics has been uncommon in the experience of this clinic. The significance of this fact is unknown. There is no question but that diabetics, particularly females, are especially susceptible to urinary tract infections. Autopsy material has confirmed the frequency of acute and chronic pyelonephritis.

Because of the increasing importance of renal disease in the management of diabetes and the unusual clinical material available in this clinic, we have undertaken a study of selected diabetic patients with renal disease in an attempt to clarify the clinical manifestations of this frequently fatal lesion. At present we know of no curative therapy. Renal or coronary artery disease represents the greatest menace to the young diabetic. There is no generally accepted means of delaying or alleviating these so-called "degenerative" diseases which eventually lead to a fatal outcome. Control of diabetes with a planned diet and insulin in the prevention of these complications has been considered of prime importance but the exact relationship between control of the diabetes and other factors, such as infection and abnormal endocrine states, has not been established. An answer to this question would be of extreme importance in the management of diabetic patients. Indeed, the diabetic patient with his known tendency to early and rapidly advancing vascular sclerosis offers an unusual opportunity for the study of both the etiology of arteriosclerosis and the factors which influence the course of this important disease. Recently Lukens¹² has described lesions similar to those characteristic of intercapillary glomerulosclerosis in the kidney of a dog kept diabetic for five years after injections of crude extract of

beef anterior pituitary. The study of vascular sclerosis is thus open to investigation in at least one species of lower animal.

PROCEDURE

In order to obtain an estimate of the relative incidence of the various types of renal complications in our diabetic population we have first studied the data available in the records of all patients discharged from the New England Deaconess Hospital in the year 1944 with a diagnosis stating or implying disease of the urinary tract. All of these admissions were of patients with diabetes. The previous records and subsequent developments were consulted and the patients were catalogued with the final diagnosis, which in many instances would be more accurate than the original clinical impression.

The data in Table II reveal an unusually high proportion of patients with the clinical manifestations of nephrosis, i.e., young patients with albuminuria, hypoproteinemia, often with edema and with clinical progression to hypertension and azotemia. To avoid the confusing term nephrosis and for reasons we shall set forth this syndrome will be referred to as intercapillary glomerulosclerosis.

Since many of the patients in this clinic have been followed for several decades, we were afforded an unusual opportunity to study the life history of their renal complications. We have, therefore, selected those patients from the 1943 to 1945 population who fulfilled the following qualifications: (1) Onset of diabetes mellitus before age thirty; (2) duration of diabetes mellitus of not less than ten years; (3) serial examinations over the course of their diabetic history extending from a period when renal function was normal to the presence of unmistakable impairment of renal function or death; (4) clinical evidence supporting a diagnosis of intercapillary glomerulosclerosis. From the three-year hospital population we have selected forty-three patients who fulfill these qualifications.

Through study of this selected group of patients we were able to evaluate the significance of duration of diabetes, of degree of control and of severity of diabetes, in addition to the chronology of onset of such specific symptoms as hypertension, albuminuria, edema, azotemia and other laboratory evidence of impairment of renal function.

JULY, 1949

The records of this group of forty-three patients were summarized in tabular form. In some instances hospital admissions were arranged in order to complete the serial study. The data have been studied and evaluated in comparison with the characteristics of the

TABLE II
SUMMARY OF DIABETIC PATIENTS DISCHARGED FROM THE
JOSLIN SERVICE IN THE PERIOD JANUARY 1, 1944
TO DECEMBER 31, 1944

	No.	Per Cent of Total
Total no. patients.....	1,708	
Male.....	685	40
Female.....	1,023	60
Patients with proven urinary tract disease.....	83	4.9

Type of Urinary Tract Disease	No.	Per Cent of Total with Renal Disease
Cystitis*.....	10	12.1
Lithiasis (of the kidney, ureter or bladder).....	10	12.1
Pyelitis and pyelonephritis.....	21	25.2
Vascular nephritis†.....	12	14.5
Nephrosis (? intercapillary glomerulosclerosis).....	17	20.5
Toxic nephritis‡.....	1	1.2
Anatomic aberrations—leading to disease.....	4	4.8
Idiopathic edema (without demonstrable renal lesions).....	1	1.2
Acute glomerular nephritis.....	2	2.4
Miscellaneous§.....	5	6.0

* This diagnosis was made only in the presence of pyuria, positive urine cultures and with a demonstrable systemic reaction, i.e., fever or urinary symptoms. If pyuria and positive cultures alone were used as the criteria, the incidence would be much higher, particularly in females.

† This diagnosis was made according to Volhard and Fahr's definition of "nephrosclerosis."

‡ In this case due to sulfonamides.

§ Including one case of toxemia of pregnancy with apparent recovery, one case of renal amyloidosis, one case of hepatorenal failure, one case of coma with anuria and one case of hematuria of unknown etiology.

1944 hospital population used as a reference group and the following attributes of the study group itself have been summarized: (1) Sex

distribution. (2) Age distribution at the time of study. (3) Age at diagnosis of diabetes and duration of diabetes. (4) Severity of diabetes. (5) Degree of control of diabetes. (6) Frequency and sequence of clinical manifestations. (7) Correlation of time of onset of clinical signs of intercapillary glomerulosclerosis with duration of diabetes and with the chronologic age of the patient. (8) Histological findings in fatal cases.

COMMENTS

Sex Distribution. Seven patients in eight cases published by Kimmelstiel and Wilson,⁷ were known to be diabetic, five of whom were females. This preponderance of females has been reported by others who have surveyed anatomic material. Henderson *et al.*¹¹ found the anatomic lesion almost twice as frequently in females as in males. In contrast, Table III illustrates that in 1944 in this hospital there was a significant disproportion between the sex incidence of the clinical syndrome of intercapillary glomerulosclerosis observed in that year when compared with the sex distribution of the entire 1944 hospital population. We found the complication twice as frequently in males despite the 3:2 preponderance of females in our hospital population.

Table IV indicates a similar preponderance of males in the entire study group.

Since the sex distribution of the seventeen patients with intercapillary glomerulosclerosis seen in 1944 is related to that of the total hospital population of which they were a part, this variation is given added significance.

Age Distribution. Previous reports concerned primarily with anatomic material have all emphasized that the most frequent occurrence of the glomerular lesions is among patients in or beyond the sixth decade. We believe that this cannot be explained as a corollary of occurrence with mild diabetes, therefore allowing longer life, but rather as a manifestation of age selection of patients when autopsy material of a general hospital is used as the source of information. Henderson *et al.*¹¹

have pointed out that the incidence of the glomerular lesions correlates better with duration of diabetes than with chronologic age. Figures 1 and 2 indicate that in the living diabetic population we have studied a high incidence of intercapillary glomeru-

TABLE III
DISTRIBUTION BY SEX OF PATIENTS WITH URINARY TRACT DISEASE—1944

	No.	Male		Female	
		No.	Per Cent	No.	Per Cent
Total discharged patients.....	1708	685	40	1023	60
Total with urinary tract disease.....	83	29	35	54	65
Total diagnosed intercapillary glomerulosclerosis.....	17	11	65	6	35

TABLE IV
SEX DISTRIBUTION OF FORTY-THREE PATIENTS DIAGNOSED AS HAVING INTERCAPILLARY GLOMERULOSCLEROSIS COMPLICATING DIABETES MELLITUS

	No.	Per Cent
Intercapillary glomerulosclerosis { Males... Females	27 16	63 37

losclerosis occurs in a considerably lower age group than is indicated in other reports.

In Figure 1 the apparent increase of renal disease in the third decade is accounted for by the presence of the patients to be discussed. The increase in the sixth decade, following five to ten years after the median age of onset of diabetes for the general population, may likewise represent the accelerating effect of diabetes upon vascular sclerosis and renal sclerosis particularly. We have insufficient autopsy data to confirm the latter point. We have not determined the age distribution of the entire hospital population for comparison. Consideration of previous reports based upon anatomic data suggests that most of those patients studied would fall in the latter age group.

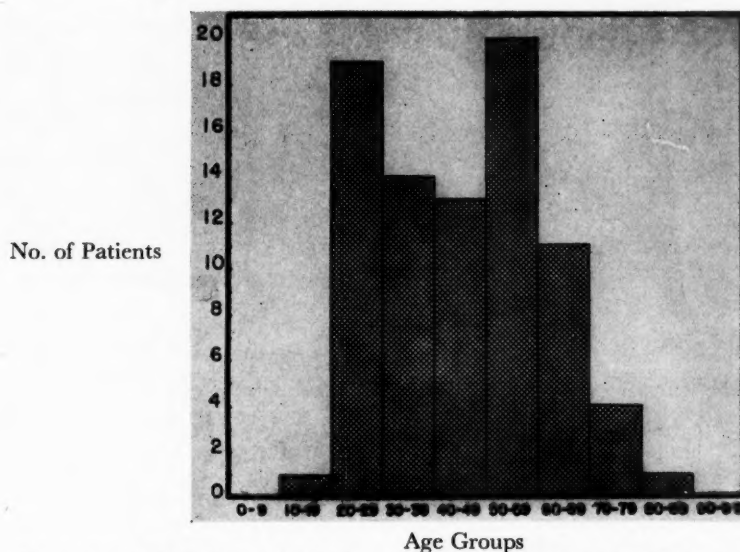


FIG. 1. Age distribution of eighty-three patients with urinary tract disease; 1944 hospital population.

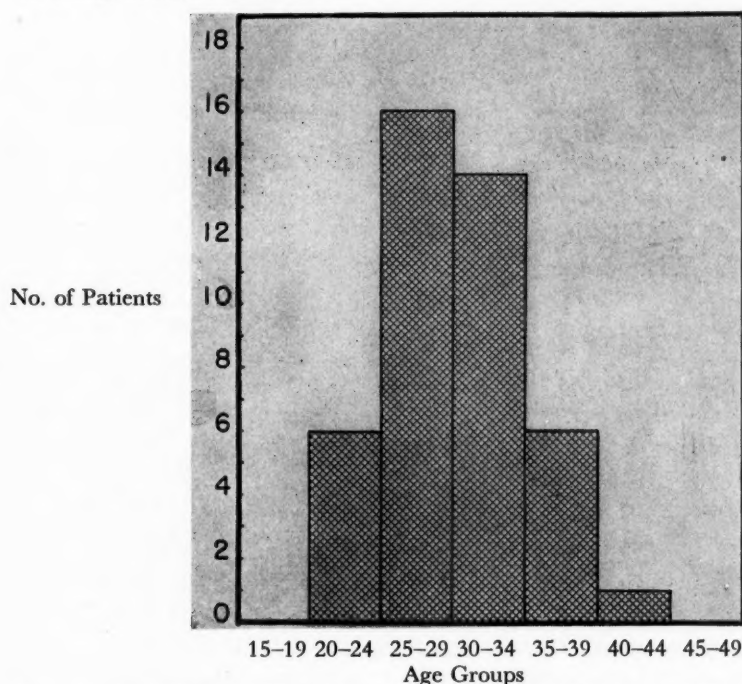


FIG. 2. Age distribution of forty-three patients with intercapillary glomerulosclerosis.

Figure 2 illustrates the age distribution at the time of study of the entire group of forty-three patients diagnosed as having intercapillary glomerulosclerosis. Since these patients are age-selected cases as just described, this distribution is not strictly comparable with the entire hospital population. However, our experience indicates that the syndrome is not found frequently in patients over forty years of age.

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Duration of Diabetes. Few of the anatomic studies have emphasized the significant relation between duration of diabetes and development of vascular complications. The records of this hospital are especially valuable because a large group of young diabetics has been followed for several decades and particular emphasis has been placed upon determination of the time of onset of diabetes mellitus. Juvenile diabetes

is in addition more easily dated because of the acute manifestations and the presence of parental observers.

In the group of forty-three patients studied the average age at the onset of the diabetes was 15.8 years and the average

TABLE V
ESTIMATE OF SEVERITY OF DIABETES MELLITUS

Severity	Daily Insulin Dose (units)	No. Patients	Per Cent of Total
1 plus	0-20	3	7
2 "	20-40	23	53
3 "	40-60	15	35
4 "	60+	2	5

duration of diabetes at the appearance of the first sign of renal disease was 14.8 years.

Severity of Diabetes. Previous reports have emphasized that renal complications occur more commonly in patients with mild diabetes. Our experience does not confirm this observation. Table v indicates that the diabetes in our series was severe, as indicated by insulin requirement.

Degree of Control of Diabetes. It is of crucial importance to the management of diabetics to know the relationship of diabetic control to development of irreversible complications. Various opinions are held.^{13,14} The answer is in part complicated by the difficulty in clinical practice of accurately determining for long periods of time the degree of control which is achieved. The outstanding facts presented by Priscilla White in her study of 192 diabetic children who survived twenty years of diabetes are: (1) Of fifty patients incapacitated by nephritis, retinitis and coronary disease 75 per cent had been in coma one or more times. (2) Of 114 patients with moderate lesions (a few retinal hemorrhages, calcified arteries) 50 per cent had had coma. (3) In twenty-eight patients without arteriosclerosis coma had been present in only 17 per cent.

Table vi lists our appraisal of the degree of control achieved in the group of patients

studied. A somewhat more objective method may be the history of diabetic coma. Of the patients studied 37 per cent were in diabetic coma on at least one occasion. In this clinic that is considerably above average. On the other hand, there is no known

TABLE VI
ESTIMATE OF DEGREE OF CONTROL OF DIABETES MELLITUS
Fair* 55 per cent
Poor* 45 per cent

	No.	Per Cent of Total
Patients never in coma.....	27	63
One episode of coma.....	8	19
Two episodes of coma.....	4	9
More than two episodes of coma.....	4	9
	43	

* Clinical appraisal based upon urine and blood glucose levels upon admission.

young patient with comparably severe diabetes who has escaped arteriosclerotic complications while maintaining poor control of his disease.

CLINICAL MANIFESTATIONS

The correlation between the clinical manifestations of renal complications in diabetes and the anatomic findings is good only when the renal lesions are far advanced. Thus Henderson *et al.*¹¹ found that intercapillary glomerulosclerosis could be predicted with a fair degree of certainty in a diabetic of long duration with albuminuria, hypertension, renal insufficiency and retinopathy. These authors found that patients with retinopathy involving the veins, with or without proliferative changes, invariably showed intercapillary glomerulosclerosis at autopsy.

Figure 3 summarizes the frequency of clinical manifestations in the patients we have studied. Since the patients were in various stages of development of the renal complication (40 per cent dead), it will be recognized that the incidence of these manifestations will increase. The universal appearance of albuminuria and hyperten-

sion is consistent with other reports. The frequency of retinitis and particularly of retinitis proliferans, equivalent to Wagener's Group IV,¹⁵ suggests a correlation between this clinical syndrome and the renal disease. Somewhat fewer of these patients exhibited cardiac signs or symptoms than in other reports. We believe this may be explained by the considerably younger age group studied. This would seem to imply that the renal vessels are more susceptible than the coronary vessels in younger patients, or the explanation may lie in the superimposition of this arteriolar disease upon the arterial sclerosis commonly seen in non-diabetic patients with advancing age, in the latter instance making the heart and great vessels more vulnerable.

Volhard and Fahr¹⁶ and later Addis and Oliver¹⁷ emphasized the importance of red blood cells in the urinary sediment in distinguishing chronic glomerular nephritis from nephrosclerosis. These and most subsequent authors agree that hematuria is infrequently found in the course of nephrosclerosis and when found the number of red cells is small. In contrast, hematuria, usually massive in amount, is characteristic of all stages of glomerular nephritis, with the occasional exception of the recovery stage when hematuria disappears before the casts and proteinuria. Proteinuria in nephrosclerosis is also generally less than in glomerular nephritis, rarely exceeding 2 Gm. per twenty-four hours and generally less than 1 Gm. per twenty-four hours. In the diabetic group studied here proteinuria was an early finding and typically averaged 3 to 10 Gm. per twenty-four hours after the first few months.

The character of the urinary sediment in diabetic patients is often affected by lower urinary tract infection but study of these patients indicated first that red blood cells or cellular casts were generally absent and when present were few in number. Casts were frequent but in small numbers and almost always of the hyaline type with typical broad, hyaline "renal failure" casts terminally.

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Edema also is infrequent in nephrosclerosis unless cardiac failure is responsible. Edema was a frequent early symptom in the diabetic group studied and in the females was often the first sign observed.

Anemia in these patients did not appear

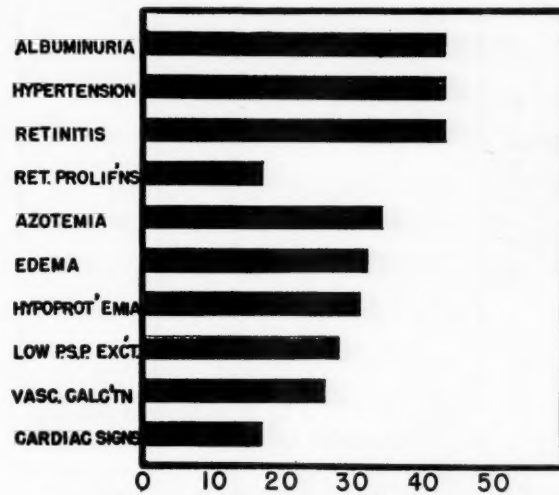


FIG. 3. Frequency of manifestations.

until late in the course of the renal disease, in contrast to the expected course of chronic glomerular nephritis. In these patients the onset of significant anemia coincided with the appearance of azotemia. In only three of the forty-three patients did the hemoglobin fall below 10 Gm. per cent or the red blood cell count below three million per cu. mm. during the course of the disease.

Despite the massive proteinuria, hypoproteinemia was a relatively late and generally terminal finding. A typical terminal value of 4 Gm. per cent with an albumin globulin ratio of 1 was found. Apparently these patients, who maintain good appetites until uremia occurs and are maintained on adequate diets, are able to synthesize new protein to compensate for the large amount lost in the urine. The lack of correlation between serum protein levels and the onset of edema was striking in contrast to the findings in nephrosis or the degenerative nephritis of Addis.

The implication of faulty cholesterol metabolism in the tendency to development of vascular sclerosis among diabetics

suggested a compilation of the serum cholesterol levels observed in this group of patients. There were twenty-two patients in the study group with adequate serial observations of the cholesterol level in the blood. With one exception, these values

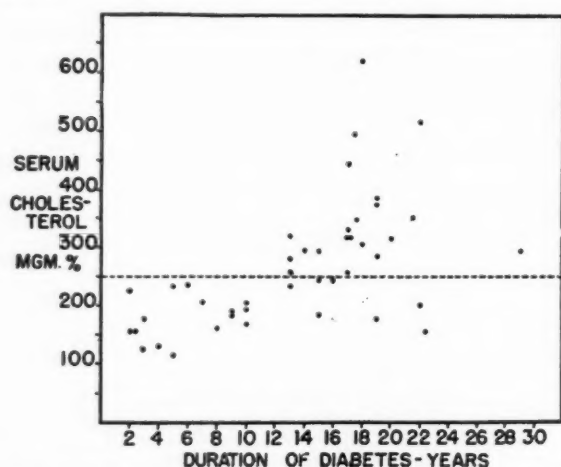


FIG. 4. Relationship of serum cholesterol to duration of diabetes in twenty-two patients with intercapillary glomerulosclerosis.

were all below the accepted maximal normal of 250 mg. per cent when the patients were first seen, and the excepted patient's level became normal within a few days after treatment with insulin. As illustrated in Figure 4 the cholesterol levels remained within normal limits for the first ten years of the disease. After this time, coinciding with the development of clinical manifestations of intercapillary glomerulosclerosis, there was an increase of serum cholesterol in all but three of the patients. We have no certain means of distinguishing cause from effect but are inclined to believe this elevation of serum cholesterol may be associated with the renal and vascular disease for two reasons: (1) The cholesterol abnormality appears almost simultaneously with or after other destructive signs or symptoms of renal complications. (2) The elevation of cholesterol correlates well with the fall in serum proteins. This inverse relationship of total serum protein concentration to serum cholesterol concentration is seen, however, in other forms of renal disease, notably nephrosis, in which vascular sclerosis is not found. The influence of

this cholesterol abnormality upon development of vascular sclerosis and intercapillary glomerulosclerosis is still to be determined.

Table VII illustrates the chronologic life history of the renal complications as manifested in this group of patients. Those pa-

TABLE VII
RELATIONSHIP OF CLINICAL MANIFESTATIONS
AND LABORATORY FINDINGS TO AGE AND
DURATION OF DIABETES MELLITUS

Manifestation	No. Patients Examined*	Average Age at Onset of Manifestation (yr.)	Average Duration of Diabetes at Onset of Manifestation (yr.)
Albuminuria.....	40	26.0	15.0
Edema.....	32	29.0	15.9
Hypertension.....	40	28.8	16.1
Impaired PSP excretion.....	28	29.5	17.2
Azotemia.....	33	33.3	17.8
Hypoproteinemia..	31	30.2	17.8
Calcification of vessels visible by x-ray.....	30	18.0

* Only those patients are included in whom the age at onset could be determined with accuracy.

tients whose records did not furnish accurate evidence of the time of onset of a particular manifestation were excluded from consideration in this tabulation.

We are led to conclude that there is a natural sequence of events in development of this renal complication. The earliest manifestation is albuminuria, at first small in amount and transient, later becoming permanent and massive. Edema is not consistently related to the level of serum proteins, hypoproteinemia developing considerably later than edema. Edema also is intermittent initially. Hypertension occurs early and in our experience is often not of extreme degree until late in the course of the disease. We have been impressed with the number of patients who exhibit loss of phenolsulfonphthalein clearance and show hyposthenuria at a late stage of the disease.

Studies are continuing in an effort to establish whether renal tubular function is

preserved after a demonstrable reduction of glomerular filtration rate. It would be of interest to know whether the anatomic specificity of the most obvious lesion determines the limitation of a specific renal function, namely, glomerular filtration.*

FATAL CASES OF RENAL DISEASE COMPLICATING DIABETES

Of the forty-three patients selected for study sixteen are now dead. Table VIII summarizes these cases.

TABLE VIII
SUMMARY OF SIXTEEN FATAL CASES OF RENAL DISEASE COMPLICATING DIABETES

Case No.	Sex	Age at Onset of Diabetes (yr.)	Duration of Diabetes at First Renal Signs (yr.)	Duration of Life after Onset of Nephrosis (yr.)	Duration of Diabetes at Death (yr.)	Age at Death (yr.)	Immediate Cause of Death	Autopsy	Presence of Lesions of I.C.G.*
6208	M	12	18	2	20	32	Pulmonary edema	x	x
4768	M	10	16	7	23	33	Cerebral embolus	x	x
7795	F	15	11	7	18	33	Renal failure	x	x
6346	M	12	9	9	18	30	Myocardial infarction	x	x
6033	M	21	12	7	19	40	Renal failure	x	x
7695	F	17	11	5	15	33	Sepsis and myocardial infarct	x	0
3761	F	9	18	3	21	30	Congestive failure	x	x
8405	M	10	10	6	20	26	Postoperative shock	x	x
2726	M	14	16	9	25	39	Renal failure	0	?
13272	M	9	9	5	14	23	Renal failure	0	?
10999	M	24	9	6	15	39	Renal failure	0	?
4746	M	13	7	11	18	31	Congestive failure	0	?
5635	F	13	7	12	19	32	Renal failure	0	?
10270	M	7	16	4	20	27	Renal failure	0	?
5036	M	9	18	2	20	29	Renal failure	0	?
7966	M	10	14	8	22	32	Renal failure	0	?
Average	..	12	12	6.4	19	32			

* Inter-capillary glomerulosclerosis.

Dolger⁴ has pointed out that calcification of peripheral vessels demonstrable by x-ray is a relatively late and inaccurate sign of vascular damage. Our evidence supports this view. However, the value of this sign is determined by the diligence with which it is sought. Our continuing studies include regular and extensive x-ray examination of the most frequent sites of calcification, notably the legs and pelvis.

* Since this article was written Corcoran *et al.* have published studies on the renal hemodynamics in inter-capillary glomerulosclerosis which tend to substantiate this hypothesis. CORCORAN, A. C., TAYLOR, R. D. and PAGE, I. H. Functional patterns in renal disease. *Ann. Int. Med.*, 28: 576, 1948.

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This group is composed of twelve males and four females, a distribution which is consistent with the preponderance of males in the entire group. The average age of the onset of diabetes was approximately 12.4 years in the fatal cases, coinciding with the observation that in children diabetes is most frequently first observed during puberty. The study group of patients did not include an unusual number of "diabetic dwarfs" or other evidences of endocrinologic disorders. The average duration of diabetes when the first renal abnormality was noted shows considerable variation. It is apparent, however, that these young patients had developed extensive vascular damage as judged by renal function in a period of 12.5 years after the onset of diabetes and are at age twenty-five

comparable in this respect with non-diabetic patients of over twice this chronologic age. In the majority of these patients the first clinical sign of renal damage was proteinuria although in a few, particularly the females, edema was the first sign. The short duration of life (average 6.4 years) after the appearance of the first signs of renal disease, although quite variable, serves to emphasize the malignancy of this complication.

There were eight autopsied cases, seven of which showed some degree of intercapillary glomerulosclerosis. In the seven cases in which the anatomic diagnosis was established the average duration of life after the first renal sign appeared was 5.9 years. The average duration of diabetes at death for this group was 19.0 years and the average age at death thirty-two years.

Cases 6208 and 4768 in Table VIII are of particular interest since these patients were identical twins. Diabetes was diagnosed at ages twelve and ten years, respectively, and the clinical courses were remarkably similar. Severity of diabetes was similar in both patients. Control of the disease was only fair in each case although neither patient was known to have been in a diabetic coma. The terminal events in case 4768 were complicated by peripheral vascular occlusions requiring amputations. Autopsy examination revealed extensive arteriosclerosis in both patients with both atherosclerotic and arteriolar changes. In case 6208 typical advanced lesions of intercapillary glomerulosclerosis were found with extensive arteriolosclerosis and atherosclerosis. There was moderate renal interstitial fibrosis and inflammation. Case 4768 showed fresh renal infarctions with extensive arteriosclerosis. The degree of arteriolosclerosis masked the typical intercapillary lesions but in some glomeruli characteristic lesions were found. These two patients with a common genetic background illustrate the anatomic variations along a single pattern which may develop in diabetes of long duration.

With the exception of case 7695 the remaining five autopsied cases all showed four distinctive lesions in the kidneys: atherosclerosis, arteriolosclerosis, interstitial inflammation with fibrosis and intercapillary glomerulosclerosis. The degree of each of these changes was variable. Far advanced arteriolosclerosis tended to obscure the characteristic changes of intercapillary glomerulosclerosis. Case 6033, on the other hand, was characterized by vascular lesions predominantly in the form of inter-

capillary glomerulosclerosis. The evidences of pyelonephritis were slight and limited to an interstitial inflammatory reaction with scattered areas of fibrosis. The distinction of the histologic lesions in these patients from the lesions of glomerular nephritis was easily apparent. However difficult the problem of determining the earliest anatomic signs of intercapillary glomerulosclerosis may be, absence of the classical signs of glomerular nephritis allows immediate elimination of this diagnosis.

Case 7695 was distinctively typical, histologically, of chronic glomerular nephritis. A moderate degree of arteriolosclerosis and atherosclerosis was also present and a small amount of interstitial infiltration indicated the presence of mild pyelonephritis. In retrospect, the clinical course of this patient should have betrayed the type of renal disease present. Although no acute episode of glomerulonephritis was recognized, the onset of massive albuminuria, hypertension and hematuria with casts was almost simultaneous. The hypertension became severe within a few months. Marked anemia appeared in the early stages. Phenolsulfonphthalein clearance fell early and within two years after the first recognized renal signs the patient was in typical uremia. Cardiac decompensation was present when edema first appeared.

The course and histologic findings of this patient thus serve to contrast the picture of chronic glomerular nephritis with that of the distinctive picture seen in the remaining cases.

Using these data as a guide we may postulate a hypothetical "typical" case which would represent the average performance of this group.

A thirteen year old child develops moderately severe diabetes requiring 40 to 60 units of insulin per day for adequate control on a regulated diet. Management of the disease is only fair and diabetic coma will probably occur. Thirteen years later at the age of twenty-six the first signs of renal damage appear, with an insidious and often intermittent proteinuria. After a few months this becomes constant and increases in amount to 3 to 10 Gm. per twenty-four hours. The urine sediment reveals numerous hyaline casts and occasionally small numbers of red blood cells. These signs are followed by intermittent

edema and hypertension, both mild in degree. Punctate hemorrhages are found in the eye grounds. In two years proteinuria, edema and hypertension are well established, the serum non-protein nitrogen is now elevated, the serum albumin fraction falls and the phenolsulfonphthalein excretion becomes moderately reduced. The patient often complains of poor vision and examination reveals retinitis proliferans—usually bilaterally. Careful x-ray examination will generally reveal calcification of peripheral vessels or occasionally of the vas deferens in males.

The terminal two to three years lead to progressive deterioration with persistent uremia, edema, hypoproteinemia and anemia. Death is usually caused by myocardial infarction, congestive failure or a result of renal failure and uremia. In the last few months the diabetes is controlled with great difficulty. The patients are often blind at death with hemorrhagic glaucomas.

The association of these characteristic clinical manifestations with the remarkable prematurity of vascular sclerosis, and particularly with the glomerular lesions previously described in diabetics of long duration, lead us to believe that the clinical course and anatomic changes represent a distinctive entity. Just as the glomerular lesions may be found occasionally in non-diabetics, so the clinical findings may suggest a true chronic glomerulonephritis and be misleading.

The relationship of this peculiar renal complication of diabetes to nephrosclerosis is not clear. The disparity in the age of the diabetic group when compared with the older patients usually seen with nephrosclerosis suggests that the two are fundamentally different diseases. However, the well known tendency of youthful diabetics to "age" rapidly, with early appearance of signs of vascular sclerosis, may make a consideration of chronologic age in these patients misleading. Indeed, the situation implies that calculation might be made using chronologic age and diabetes duration which would allow one to arrive at a

"true age" from these data. Until and unless this is done it would seem fallacious to draw conclusions from chronologic age data.

Duration of the disease, nature of the urine sediment, mild anemia and associated cardiovascular changes suggest the similarity of this disease of diabetics to the malignant form of nephrosclerosis seen in non-diabetics. However, the early onset of edema and the massive proteinuria serve to distinguish the two forms of renal disease. That these distinctions represent the influence of the youth of the patient substratum and other unknown influences of associated endocrine abnormalities remains uncertain. Until these factors are clarified it seems profitable to consider intercapillary glomerulosclerosis as a distinct entity both clinically and pathologically.

We know of no preventive measures other than continual and careful control of the diabetes with insulin, diet and exercise. Therapy after the disease has appeared is symptomatic. Perhaps the most hopeful aspect of this problem lies in the suggestions and material which it contributes to the study of arteriosclerosis and the biologic phenomena of aging.

SUMMARY

1. The records of all patients with urinary tract disease admitted over a period of one year to a hospital medical service specializing in diabetes have been studied and the types of renal disease classified.

2. The incidence of a characteristic syndrome consisting of proteinuria, edema, hypertension and retinitis occurring in young people with diabetes of long duration, is determined. Although the prognosis in the past has been grave, hope for future improvement by better control of diabetes and its complications is well founded.

3. A group of forty-three patients exhibiting this renal complication of diabetes has been studied and the usual course of the disease described.

4. The correlation of these clinical manifestations with the distinctive anatomic lesions often seen in the renal glomeruli of diabetic patients is discussed.

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Experiences with the Kolff Artificial Kidney*

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IN March, 1947, Dr. W. J. Kolff brought to Mt. Sinai Hospital an artificial kidney devised by him.¹ We are presenting our experiences in the management of six patients who have been treated with this artificial kidney. At first we were reluctant to expose our patients to a new form of treatment with which we were relatively unfamiliar. Moreover, we had learned that a poor prognosis in acute toxic nephrosis often proves to be unwarranted; satisfactory results obtained by conservative management of such patients have been recorded elsewhere.²⁻⁴ We have stressed the possibility that diuresis may occur spontaneously. However, if this apparatus could contribute to the maintenance of metabolic equilibrium and sustain the patient until spontaneous diuresis should occur, it would be a valuable adjunct in the treatment of acute anuria.

All six patients who were treated by use of the artificial kidney were critically ill. The first four were dying of uremia. All conservative measures had been ineffective. These patients made it possible to test the capabilities of the apparatus without incurring risk of influencing the clinical course adversely. As the functional capacity of the machine and its efficacy were established the last two patients, although critically ill, were treated earlier than the others and they recovered. It is impossible to state whether spontaneous recovery would have occurred without use of the apparatus.

The possibility of removing various toxic products by dialysis has interested investigators for many years.⁵ Some have advo-

cated use of viable tissue membranes for dialysis.^{6,7} Peritoneal lavage has recently been revived by Fine and Seligman.^{8,9} The difficulties of the method are well known to those who have attempted this form of dialysis;¹⁰ they include peritonitis, obstruction of the inlet tube, difficulty in maintenance of flow and the long period of time involved. Use of an exteriorized intestinal loop and irrigation by a Miller-Abbott tube, and colonic irrigation have also been attempted, with varying degrees of success.¹¹⁻¹⁴

In 1912 Abel, Rowntree and Turner dialyzed the blood of living animals through collodion tubes, using hirudin as an anticoagulant.⁵ Haas, Necheles and Thalhimer¹⁵ extended these experiments. Kolff¹² described the first mechanical apparatus to permit continuous extracorporeal dialysis. Subsequently Alwell^{16,17} and Murray¹⁸ presented other devices. They have all taken advantage of the availability of cellophane and the reliability of heparin. Their machines make possible the dialysis of regulated volumes of blood outside of the body without danger of infection or coagulation. Each has attempted to achieve a maximum surface area of exposed blood per unit volume. Our experience is confined to the apparatus of Kolff.

METHODS AND MATERIALS

The basic mechanisms of the artificial kidney devised by Kolff are illustrated in Figures 1 and 2. The blood is rendered incoagulable by heparin. The blood is then delivered under the drive of arterial pressure to the coils of cellulose

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acetate (Visking) tubing tightly wound about a rotating drum. The capacity of this machine is 500 to 700 cc. of blood. A special coupling serves as a conduit to enable the blood to enter and leave the cellulose acetate tubing without interfering with the rotation of the drum. Prior

the individual needs of the patient. In addition a shunting circulation is provided which permits circumvention of the dialyzing portion of the apparatus and enables direct intravenous administration of drugs, blood, etc., should the need arise. The glass arterial and venous can-

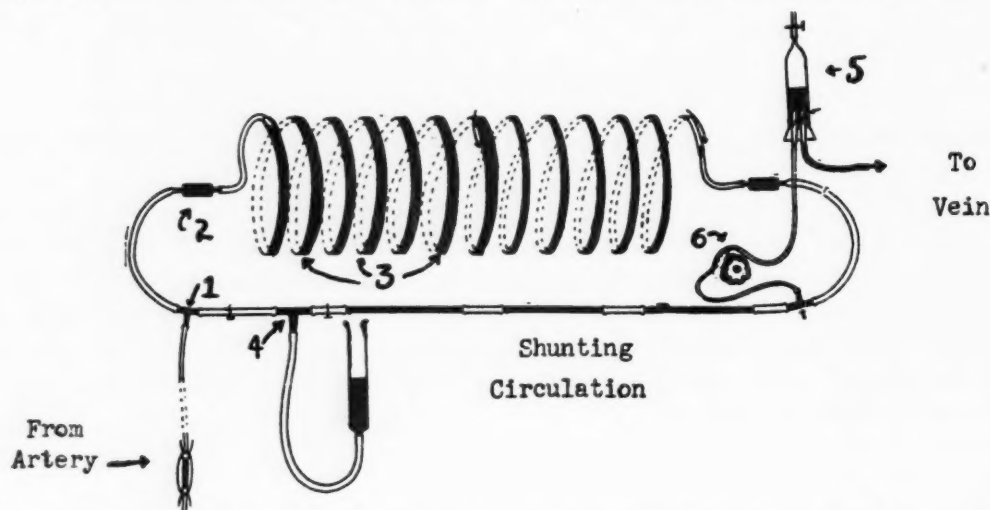


FIG. 1. The circulation of the artificial kidney (modified after Kolff). The blood leaves the radial artery and is led by connecting tubes (1) through the special coupling (2) into the coils of cellulose acetate (3) which are wound around the rotating drum. Fluids or drugs may be administered through a special connection (4) which allows the administered fluids either to pass through the kidney or be shunted directly into the vein of the patient. After dialysis the blood passes to a clot remover and air trap (5) before returning to the patient's vein. A mechanical pump (6) facilitates the emptying of the last coils of the artificial kidney.

to the start of treatment the tubing is filled either with heparinized whole blood or normal saline solution, depending on the hematologic needs of the patient. The blood from the radial artery displaces the contents of the system of tubing. A milking pump at the end of the system facilitates return of the blood to the patient's vein via an air trap and clot remover. While the blood is passing through the coils of cellulose acetate, the rotation of the drum intermittently exposes it to 100 L. of bath fluid which contains 0.6 per cent sodium chloride, 0.2 per cent sodium bicarbonate, 0.04 per cent potassium chloride and 1.5 per cent glucose. Calcium is not added to the bath since a precipitate of calcium carbonate would form. Consequently calcium gluconate is administered intravenously at regular intervals to replace the dialyzable calcium which escapes into the bath. Thus, under the continued influence of arterial pressure, gravity and a milking pump, blood is led from the radial artery to a brachial vein via an extrinsic vasculature made of cellulose acetate. During circulation it is exposed to a bathing solution which may be varied according to

nulae prescribed by Kolff were found to be unnecessary precautions against coagulation and were discarded in favor of ordinary metal intravenous needles. At regular intervals chemical analyses were made of blood entering and leaving the apparatus as well as of the bath fluid. These included blood urea nitrogen (Van Slyke and Cullen), creatinine (Folin and Wu), uric acid (Brown), glucose (Folin and Wu), serum protein (Kagan), serum chloride (Van Slyke and Sendroy), icterus index (Newburger), bilirubin (van den Bergh), calcium (Kramer and Tisdall), inorganic phosphorus (Kuttner and Lichtenstein), sodium (Butler).¹⁹

CASE REPORTS

CASE I. E. R. is a Puerto Rican woman twenty-five years of age. On January 5, 1948, twenty-one days before admission to the Mount Sinai Hospital, she was raped. On the evening of January 21st, when the anticipated menstruation failed to occur, she inserted 5 sublimates of mercury tablets (2.5 Gm.) into the vagina in order to induce abortion. Several hours later abdominal pains appeared. By the

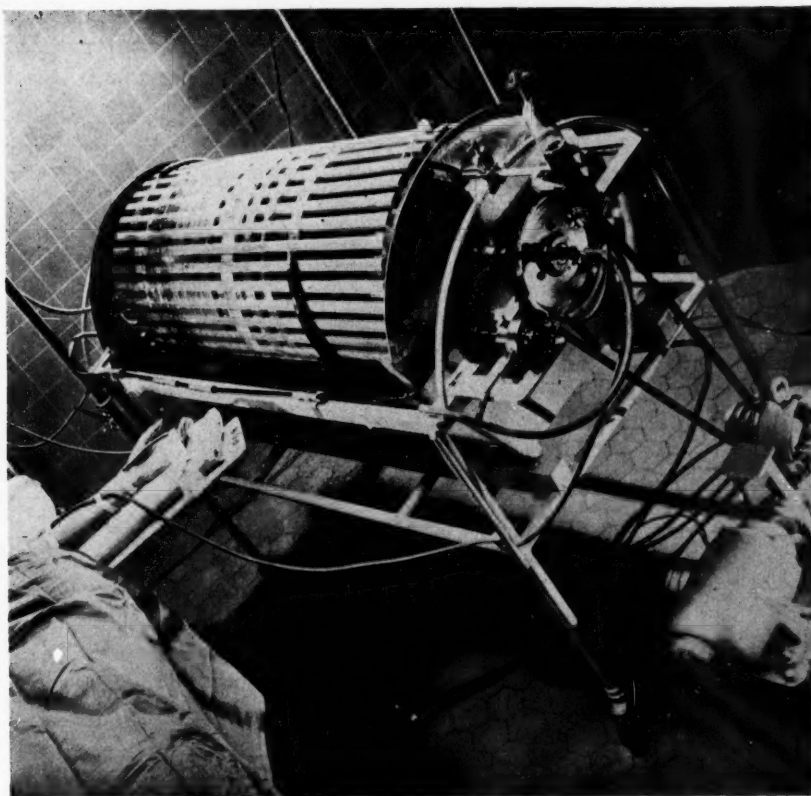


FIG. 2. The artificial kidney in use.

next morning she was acutely ill, with abdominal pain, bloody diarrhea, frequent vomiting and profuse vaginal bleeding. On January 23, 1948, she was admitted to the gynecologic service of another hospital. The temperature was 100.8°F., the pulse was 86 and the respirations 20 per minute. Blood pressure was 112 mm. Hg systolic and 84 mm. diastolic. Intense vulvovaginal edema and necrosis were present. At this time analyses revealed a hemoglobin of 16 Gm., 23,600 white blood cells with 73 segmented and 22 non-segmented leukocytes and 7 lymphocytes. The serum non-protein nitrogen was 75 mg. per cent. Bloody diarrhea and vomiting continued. Pain, swelling and tenderness of the joints of the fingers appeared and progressed. Twenty-four hours after admission it was noted that the patient failed to urinate. No urine could be obtained by catheter. A history of anuria since January 22nd was then elicited. The patient was thereupon transferred to the Mount Sinai Hospital on January 26th for treatment with the artificial kidney. Up to this time she had received approximately 7,000 cc. of fluid by vein and hypodermoclysis.

Examination revealed a poorly developed, poorly nourished, semicomatose Puerto Rican

woman in acute distress. She was vomiting coffee-ground material and blood was oozing from her mouth and gums. She looked pale and her face was edematous. The temperature was 98.2°F.; the pulse was 90 and the respirations 18 per minute. Moderate bilateral conjunctivitis and chemosis were present. The upper jaw was edentulous with inflammation and necrosis of the gums; a black line was present at the gingivodental margins of the gums of the lower jaw. The tongue and mouth were inflamed and contained necrotic and exudative zones. The lungs were clear. The heart appeared normal. The blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. The abdomen was diffusely tender. The liver was palpable 1 cm. below the right costal margin and had a smooth, non-tender edge. The labia majora and minora as well as the vagina were swollen, red, covered with exudate and focally necrotic. The urethral meatus was identified with difficulty.

Examination of the blood revealed 8.5 Gm. of hemoglobin, 20,500 white blood cells with 98 per cent polymorphonuclear leukocytes, 21 per cent of the leukocytes were non-segmented. Urine (4 cc.) were obtained by catheter and contained 4 plus albumin, many red blood

cells, 10 to 15 white blood cells, many epithelial cells and rare granular casts.

Chemical examination of the blood revealed a carbon dioxide content of 26 volumes per cent; non-protein nitrogen 150 mg. per cent;

treatment with the artificial kidney was started and was continued for six hours. Heparin (100 mg.) was given into the vein and another 100 mg. was introduced into the apparatus at the onset of treatment. Four hours later 50 mg.

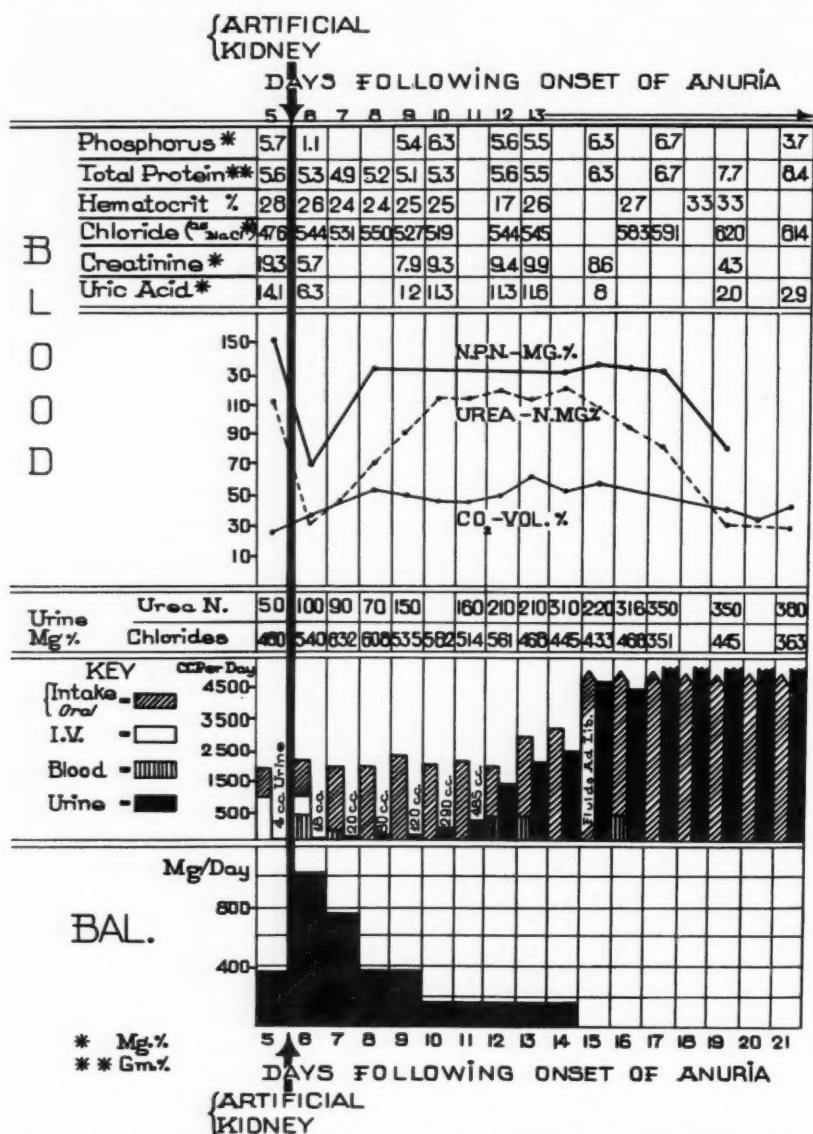


FIG. 3. Case 1. Course in hospital prior to and following the use of the artificial kidney.

urea nitrogen 110 mg. per cent; other significant chemical data are included in Figure 3.

The patient was given 5 per cent glucose in normal saline intravenously to replace fluids lost in vomitus and stool. One hundred seventy-five mg. 2,3 dimercaptopropanol (BAL) was given intramuscularly at regular intervals as indicated in Figure 3. She was also given 25,000 units of penicillin every three hours to combat infection. At 11 P.M. on the day of admission

was again administered intravenously. This dosage sufficed to maintain the clotting time of the blood (Lee and White) from one to four hours during the treatment. All observers agreed that she improved markedly during this time. She became less restless, better oriented and was able to request and retain oral fluids. The response of the blood to dialysis and the amounts of each constituent removed from the blood and found in the bath fluid are indicated in Table I.

There was evidence of slight hemodilution as manifested by the fall in hematocrit and serum protein level after treatment. There was a precipitous drop in blood non-protein nitrogen, urea nitrogen, phosphorus, creatinine and uric acid. The serum sodium levels were 122.0

chromogen level at the end of six hours was 84 mg. per cent. The carbon dioxide content of the blood was not appreciably altered during treatment and remained at 26 volumes per cent. The 100 L. of bath fluid following dialysis contained 24 Gm. of urea nitrogen, 6.7 Gm. of uric

TABLE I

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE I. Upper chart: Chemical analysis of blood entering the artificial kidney from the radial artery (A) and leaving the artificial kidney (B) to re-enter the general circulation via the brachial vein. Serial determinations were made at hourly intervals. Note the decrease in dialyzing efficiency of the kidney following the accumulation of retention products in the bath fluid. The efficiency again rose following change in bath water at the end of four hours. The total protein did not vary appreciably.

Lower chart: Chemical contents of bath fluid following six hours of dialysis. Bath water was completely replaced after four hours of dialysis. As above, values are expressed per 100 cc. of solution. The bath contains 100 L. of fluid as indicated in the text.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hematocrit
Control*	100	14.1	19.3	5.7	5.6	3	28
1 hour { A†	116	13.4	14.1	6.0	5.3	4	29
{ B‡	26	8.5	6.2	4.3	5.5	4	29
2 hours { A	86	12.9	15.5	4.4	5.0	9	29
{ B	36	8.2	7.9	2.0	5.3	7	
3 hours { A	68	10.7	13.5	2.3	5.6	12	
{ B	40	7.2	7.1	1.2	5.3	12	
4 hours { A	50	8.1	11.0	1.4	5.6	13	26
{ B	36	5.7	7.1	1.1	5.1	13	
5 hours { A§	48	9.6	9.6	1.6	5.3	14	25
{ B	14	3.7	4.5	0.9	5.5	14	
6 hours A	30	6.9	5.7	1.5	5.3	14	26

Contents of Bath Fluid (mg. %)					
	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein
Initial four hours§	19	3.6	7.3	0.6	3.6
Final two hours	5	3.1	2.4	0.4	2.9
Total	24	6.7	9.7	1.0	6.5

* One-half hour before start of treatment with artificial kidney.

† Blood sample from radial artery en route to machine.

‡ Blood sample from machine following dialysis en route to brachial vein.

§ Bath fluid was completely replaced by fresh solution after four hours.

mEq./L. before treatment and 132.4 mEq./L. after treatment. The serum chloride (as sodium chloride) rose from 94 mEq./L. before treatment to 100 mEq./L. at the end of treatment. Slight hemolysis was manifested by yellow discoloration of the serum and a progressive rise in icterus index from 3 to 13 during the six-hour period. Serum hemo-

acid, 9.7 Gm. of creatinine, 1.0 Gm. of phosphorus and 6.5 Gm. of protein. No mercury could be identified in the bath fluid.²⁰ At the close of treatment with the artificial kidney she was given 300 cc. of 5 per cent sodium bicarbonate to combat acidosis.

Subsequent to treatment with the artificial kidney she was given a high-carbohydrate,

high-fat diet containing no protein. After the first two days she was able to retain the equivalent of at least 1,500 calories per day. Fluids were administered almost exclusively by mouth except for occasional whole blood transfusions as indicated in Figure 3. The amount of fluid consisted of 1,000 cc. per twenty-four hours to compensate for insensible water loss plus the equivalent of the fluid lost by diarrhea and vomiting. The amounts of oral sodium chloride and sodium bicarbonate were varied according to the serum chloride and carbon dioxide content but averaged approximately 4 Gm. of sodium chloride and 16 Gm. of sodium bicarbonate per day.

Diarrhea and vomiting persisted for four days following use of the artificial kidney, gradually decreasing in frequency and content. The ulceronecrotic lesions of the buccal and vaginal mucous membranes responded sluggishly to local applications but gradually improved. On the eighth and ninth days following onset of anuria, pretibial and facial edema appeared but spontaneously subsided. On the eighth day after use of the artificial kidney she appeared more rational, with only occasional disorientation and periods of delusion and paranoia. She responded well to questioning and appeared to be convalescing well.

The urinary output increased gradually until the twelfth day following onset of anuria when the output approximated the intake. The urine was voided through a markedly inflamed area and the significance of albumin, red cells and white cells was difficult to determine. Granular casts were carefully sought but only rarely found during the period of observation. The urea nitrogen of the urine rose slowly to a maximum of 380 mg. per cent. The urinary chlorides varied from 351 to 632 mg. per cent (measured as sodium chloride). The specific gravity of the urine did not fall below 1.010 or rise above 1.012. On the fifteenth day following onset of anuria she was allowed fluids *ad libitum* and following the seventeenth day the urinary output constantly exceeded 4,500 cc. per twenty-four hours.

Following treatment with the artificial kidney, the blood non-protein nitrogen and urea nitrogen showed a parallel rise. Serum phosphorus, uric acid and creatinine also rose. The serum chlorides and carbon dioxide content were readily controlled by oral administration of sodium chloride and sodium bicarbonate.

Despite the adequacy of urinary output on the twelfth day following onset of the anuria and subsequent diuresis, the blood urea nitrogen, non-protein nitrogen, creatinine, uric acid and phosphorus only gradually returned to normal.

On the twelfth day following treatment with the artificial kidney the patient began to menstruate. She became hypomanic. The agitation failed to subside, paranoia supervened and delusions and hallucinations were expressed which centered around the events which had initiated the present illness. It became necessary to send the patient elsewhere for psychiatric care. A later report by Dr. R. E. Blaisdell, Rockland State Hospital, Orangeburg, N. Y., indicated that analyses made on March 5th showed the following: urea nitrogen, 13 mg. per cent; creatinine, 1.4 mg. per cent; uric acid, 2 mg. per cent; non-protein nitrogen, 30 mg. per cent. The specific gravity of the urine was 1.013.

Comment. In this instance the self-administered dose of mercury bichloride was especially large. The 2.5 Gm. instilled into the vagina remained *in situ* until completely absorbed. The subsequent symptoms were those of severe systemic mercurialism.

The patient was admitted to the Mount Sinai Hospital on the fifth day of anuria. The clinical manifestations were those of uremia, acidosis and dehydration. All observers agreed that the patient was virtually moribund. She was given BAL and intravenous alkali prior to the artificial kidney. She was treated with the artificial kidney on the day of admission. During the process of dialysis she appeared to improve and become more rational. The artificial kidney functioned well mechanically. There was a precipitous fall in non-protein nitrogen, urea nitrogen, creatinine, uric acid, and phosphorus as indicated in Table 1. Calcium gluconate (1 Gm.) was administered intravenously at hourly intervals to replace the calcium lost by dialysis. The bath fluid at the end of the treatment was found to contain a total of 24 Gm. of urea nitrogen, 6.7 Gm. of uric acid, 9.7 Gm. of creatinine and 1 Gm. of phosphorus. Protein (6.5 Gm.) were also present in the bath indicating slight permeability of the

membrane. The level of serum proteins was not appreciably altered. The hematocrit decreased slightly. Slight hemolysis was noted as the icterus index increased from 3 to 14, serum bilirubin from 0.2 and 0.5 mg. per cent and the van den Bergh reaction became delayed positive.

The subsequent management of the patient corresponded to that previously outlined.² An attempt was made to increase gradually the intake of a high-carbohydrate, high-fat, protein-free diet in order to supply adequate caloric intake. Electrolyte balance was maintained by oral administration of sodium chloride and sodium bicarbonate.

Adequate urinary output was established on the twelfth day after the onset of anuria and seven days following use of the artificial kidney. Figure 3 illustrates the gradual fall in the serum levels of non-protein and urea nitrogen despite diuresis due to the lack of renal concentrating capacity. During convalescence urea nitrogen concentration of the urine remained low. The urine chloride concentration was relatively constant—an indication of the inability of the tubules to vary the excretion of chloride in accord with the body need. The leukocytosis gradually receded and fewer transfusions were required to maintain the hemoglobin level.

Identification in this instance of any specific agent as responsible for restitution of kidney function is not possible. BAL administered more than three hours after the application of mercury is reported to have little effect on the outcome.²¹ In this patient it was started on the fifth day of anuria. We have stressed previously that patients with mercury intoxication or any type of lower nephron nephrosis²² may survive the toxic injury if electrolyte balance is maintained and circulatory embarrassment is avoided. The previously recommended measures² were again used in this case and unquestionably contributed materially to her recovery. During treatment with the artificial kidney all were impressed by the apparent innocuousness of the procedure and the clinical as well as chem-

ical improvement manifested by the patient. It is believed that the artificial kidney may have provided additional time for spontaneous improvement to occur.

CASE II. W. M., a thirty year old male who on April 1, 1948, was exposed in a small closed room to intense carbon tetrachloride fumes for five hours. After leaving the room he felt "drunk." The next day generalized muscular aches, anorexia, oliguria, and bilateral costovertebral angle pain appeared. These symptoms progressed and on April 4th he was hospitalized elsewhere. Examination revealed him to be acutely ill with slight scleral icterus. The temperature was 100°F., pulse 72 per minute and respirations 20 per minute. The blood pressure was 144 mm. Hg systolic and 90 diastolic. Tenderness was present in the mid-epigastrium and in both costovertebral angles. There was moderate anemia (10.5 Gm.). The urine contained moderate amounts of albumin and microscopic examination revealed many red blood cells. There was no choluria; the urinary urobilinogen was normal. The icterus index was 19. The cephalin flocculation test was strongly positive. The serum cholesterol was 118 mg. per cent with 63 per cent esters. Oliguria persisted, anuria ensued on April 8th. The blood urea continued to rise. Parenteral fluids were cautiously administered to replace fluids lost by vomiting and insensible loss. Methionine, choline and parenteral vitamins were given to combat hepatic injury. On April 9th pulmonary and systemic hypertension appeared, and following phlebotomy he was transferred to the Mount Sinai Hospital.

On admission he was found to be acutely ill, with a uriniferous odor to his breath. The sensorium was cloudy. The blood pressure was 148 mm. Hg systolic and 90 diastolic. Bilateral subconjunctival hemorrhages were present and were ascribed to repeated episodes of vomiting. Clotted blood was present in the nares. The heart and lungs were normal. The abdominal viscera were not palpable. The hemoglobin was 10.5 Gm. There were 10,450 white blood cells with a shift to the left of the leukocyte series. There were 290,000 platelets. The blood non-protein nitrogen was 170 mg. per cent; urea nitrogen 108 mg. per cent; serum chlorides (as sodium chloride) 423 mg. per cent; carbon dioxide content 59 volumes per cent and hematocrit 39 per cent. Clotting time, bleeding

TABLE II

CASE II: Course of patient with carbon tetrachloride intoxication prior to and following onset of diuresis. Artificial kidney was used on tenth and sixteenth days of illness. Frequent whole blood transfusions were administered following onset of diuresis to overcome the anemia and neutralize the prothrombin deficiency.

Day of Illness	Vol- ume (cc./ 24 hr.)	Urine		Blood		CO ₂ Con- tent (vol. %)	Hema- to- crit (%)	Blood		Weight (pounds)	Blood Pres- sure (mm. Hg)	Vomi- tus (cc./ 24 hr.)	
		Urea Nitro- gen (mg. %)	Chlo- rides (NaCl) (mg. %)	Urea Nitro- gen (mg. %)	Crea- tinine (mg. %)			Hemo- globin (Gm. %)	Xantho- proteins (units)				
4	100	136.5	144/90	0	Hospitalized elsewhere; hematemesis; ic- terus; oliguria
5	100	63	150/70	125	Epistaxis; rational and alert; anorexia
6	100	65	18	41.4	140/94	350	Drowsy; blood-tinged enema
7	70	65	...	43.3	140/90	475	Loin pain
8	0	95	...	37.6	142/88	825	Phlebotomy
9	180	270	117	109	15.2	59	29	10.5	...	140.5	170/100	317	Transferred to Mt. Sinai Hospital; uremic; cloudy sensorium; prothrombin deficiency
10	120	240	59	108	...	28	28	10.5	110	140.0	160/100	960	Artificial kidney
11	72	120	389	69	...	36.5	27	...	80	...	150/80	1210	Comfortable; alert
12	90	150	304	71	16.5	55	27	8.5	...	136.5	158/86	400	Drowsy
13	72	170	280	73	18.6	62	25	8.0	86	138	130/80	1055	
14	96	200	236	86	...	53	29	10.0	104	138.5	144/90	1000	
15	119	120	386	92	18.1	62	30	9.8	116	136	148/100	1769	Persistent vomiting; drowsy; irritable
16	200	180	351	98	...	54	30	9.0	125	...	130/90	135	Artificial kidney
17	270	250	397	53	...	62	27	7.2	101	...	130/80	760	Oozing from wound sites; fresh whole blood
18	604	230	316	129	160/90	950	Comfortable; alert
19	1193	250	293	89	...	52	18	8	129	125	140/80	1625	
20	2278	360	375	98	...	66	20	6.0	116	124	150/90	400	Cellulitis of foot
21	2527	360	222	98	7.3	...	123	150/88	0	
22	2653	520	211	91	30	9.2	150/98	0	
23	2652	570	175	105	...	41	33	...	66	...	160/100	235	
24	2249	660	117	104	9.8	...	36	10.0	130/88	1060	
25	2228	750	93	78	...	52	128/88	370	Cellulitis resolving
26	2370	720	105	36	11.0	152/88	0	
27	2378	710	117	48	...	61	38	...	31	116	122/88	200	Eating well
28	2202	690	152	40	...	66	34	9.0	...	117	140/90	0	
29	2465	640	175	42	33	10.2	...	117	135/90	0	Out of bed
30	3705	...	198	38	38	10.6	...	119	130/80	0	
31	3260	...	222	38	...	52	38	10.8	...	120	130/80	0	
32	2840	...	270	32	38	11.0	...	120	126/80	0	
33	2160	28	32	12.2	...	122	122/80	0	

time, clot retraction and tourniquet test were all normal. The cephalin flocculation and thymol turbidity tests were negative. The icterus index was 2. The prothrombin activity was found to range from 17 per cent to 50 per cent of normal.

In the twenty-four hours following admission

effective in removing retention products from the blood (Table III), diuresis did not ensue and uremia again gradually became manifest. On April 16th he was again treated with the artificial kidney. (Table IV.) The same amount of heparin was administered as on the previous

TABLE III

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE II: Chemical analysis of blood and bath fluid during initial treatment with artificial kidney. Bath fluid completely changed after four hours. Phenols were found in all bath fluids.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hemato-crit
0 hours	108	11.3	15.2	4.1	6.5	3	28
2 hours { A	80	11.5	28.3	4.0	6.3	3	30
{ B	30	8.0	15.0	3.1	6.7	3	
4 hours { A	76	10.0	25.2	2.9	6.1	3	28
{ B	34	7.6	16.4	2.6	6.0	3	
6 hours { A	54	8.3	23.2	3.1	5.7	3	26
{ B	14	5.5	10.3	1.8	6.7	3	

Contents of Bath Fluid (mg. %)					
	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein
2 hours.....	18	2.3	6.2	1.4	2.2
4 hours.....	27	2.8	8.5	3.1	4.3
6 hours.....	7	1.0	3.9	1.0	4.0
Total.....	34	3.8	12.4	4.1	8.3

180 cc. of bloody urine were obtained by catheter. The urine was acid (pH 5); the specific gravity was 1.016. Moderate amounts of albumin were present and many red blood cells and few white blood cells were found on microscopic examination.

Vitamin K (4.8 mg. hykinone daily) failed to return the prothrombin time to normal. He was treated for six hours on April 10th with the artificial kidney. Heparin (100 mg.) was injected into the venous cannula; 100 mg. were injected into the arterial cannula leading to the machine; 50 mg. were administered after two hours to maintain the prolonged coagulation time. He remained comfortable during the period of dialysis; the blood pressure did not vary significantly. There was no evidence of hemorrhage.

His course following the initial treatment is outlined in Table II. Although dialysis was

occasional. However, oozing of blood appeared from abraded areas about the mouth and nose and after six hours the dialysis was terminated. Toluidine blue, 3 mg./Kg., and whole blood were administered to neutralize the heparin. The oozing persisted (even though the coagulation time of the blood rapidly returned to normal) and was ascribed to the prothrombin deficiency.

The subsequent course of the patient was uneventful except for persistent vomiting which slowly subsided. Following the second treatment with the artificial kidney, there was a progressive increase in the daily volume of urine. (Table II.) By the twentieth day of illness more than 2,000 cc. of urine were being voided daily. The urine which had been grossly bloody on admission became free of red blood cells; casts were rare at all times. Albuminuria diminished; the pH of the urine became less fixed. The con-

centration of urea nitrogen in the urine gradually rose and the selective elimination of chlorides reappeared. The specific gravity of the urine varied slightly from 1.010. The azotemia slowly subsided as restoration of kidney tubular function occurred.

taneously exposed to lesser concentrations of the vapors, was admitted elsewhere because of hematemesis and jaundice. He was discharged after ten days, free of symptoms, with no evidence of renal damage.

TABLE IV

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE II: Chemical analyses of blood and bath fluid during second treatment with artificial kidney. Bath fluid changed after four hours. Phenols were present in the bath fluid after dialysis. The xanthoprotein concentration of the blood fell following dialysis.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hemato-crit	CO ₂ Content (vol. %)
0 hour	85	5.6	27.2	7.5	7.2	3	30	
2 hours {A	71	4.3	26.4	7.1	7.4	3	30	35.5
{B	24	2.3	16.1	5.0	7.4	3	..	30.0
4 hours {A	32	3.2	22.9	4.0	7.4	3	27	39.4
{B	13	1.9	11.1	3.0	7.0	3	..	32.6
6 hours {A	35	2.5	19.8	3.0	7.4	3	25	40.9
{B	19	1.8	12.0	2.5	7.0	3	..	31.7

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein	CO ₂ Content
2 hours	10	1.2	4.8	0.8	0	54.6
3 hours	23	1.6	8.9	1.7	10	50.9
6 hours	18	1.4	7.8	1.0	12	
Total	41	3.0	16.7	2.7	22	

The patient was remarkably comfortable during the entire period of renal insufficiency. Daily records were kept of fluid loss and cautious replacement served to maintain hydration as well as adequate carbon dioxide and chloride contents of the serum. Whole blood and washed red blood cells were used to combat anemia.

Comment. In this patient the nephrotoxic effects of carbon tetrachloride poisoning dominated the clinical picture. Hepatic injury was manifested by the transient icterus, bleeding due to persistently reduced prothrombin activity and abnormal retention of bromsulfalein in the blood; there was also no increase in prothrombin activity following administration of vitamin K. The patient's co-worker, who had been simul-

The patient was treated with the artificial kidney on the tenth and sixteenth days of illness. Both treatments were effective in eliminating retention products from the blood stream. (Tables III and IV.) The serum chlorides rose following the dialysis; carbon dioxide escaped from the blood during its exposure to the bath fluid. Phenols and xanthoproteins passed from the blood into the bath fluid.

The clinical course of the patient was characterized by freedom from uremic manifestations despite the long period of renal insufficiency. Following the onset of polyuria on the twentieth day of illness, azotemia gradually subsided. (Table II.) Recovery of normal tubular function evolved

slowly. It is believed that in this instance the artificial kidney served as a temporizing measure which potentiated spontaneous restoration of kidney structure and function.

CASE III. B. C., a sixty-three year old white man had had prostatism since 1933. Prior to hospitalization the urine was normal on repeated analyses. The blood pressure regularly averaged approximately 120 mm. Hg systolic and 80 diastolic. On May 1, 1947, cystoscopy was performed and the patient was admitted to another hospital in preparation for prostatectomy. On May 2 a Foley catheter was introduced for drainage and lavage. Twelve hours later the patient withdrew the catheter because of local irritation. His temperature rapidly rose to 106.8°F. He was given 1 Gm. of sulfadiazine by mouth and one intramuscular injection of penicillin. However, in the next twelve hours he voided only 100 cc. of bloody urine; sulfadiazine was discontinued. Fluids were given parenterally in large quantities; pulmonary edema ensued and was treated by phlebotomy and digitalization. Anuria persisted from May 2nd to May 7th when he was transferred to the Mount Sinai Hospital. The blood urea nitrogen had now risen to 102 mg. per cent, the creatinine to 7 mg. per cent; the carbon dioxide combining power was 32 volumes per cent. There was moderate anemia, leukocytosis and shift to the left of the white cell series.

On physical examination the patient was seen to be a well developed, obese, semistuporous male. He was restless, with spasmodic body twitchings and hyperirritability to minimal stimuli. The tongue was dry. Excoriations were present about the mouth and face. The veins of the neck were distended. The chest was emphysematous and moist rales were audible in both pulmonary bases. The respiratory rate was 28 per minute. The heart appeared enlarged to the left by percussion. The rhythm was regular with a rate of 100 per minute. The blood pressure was 105 mm. Hg systolic and 60 diastolic. The liver was enlarged 3 cm. below the right costal margin. Hepatojugular reflux was present. Moderate anascarca was present. The prostate was smooth, uniformly enlarged and approximately twice the normal size. A Foley catheter was in place.

On admission 30 cc. of one-sixth molar sodium lactate solution was given intravenously. A scout film of the abdomen revealed no evidence

of calculi. The Foley catheter was removed. Cystoscopy on May 7th revealed that the bladder was diffusely inflamed, the mucosa being lined with shreds of muco-pus. The ureteral orifices could be seen but catheters could only be passed for a distance of 0.5 cm. on each side. The lateral lobes of the prostate were found to be enlarged and met in the midline. The Foley catheter was replaced.

The repeated manipulations including cystoscopy rendered inadvisable the heparinization required in use of the artificial kidney. Peritoneal lavage was deferred because of the marked degree of debility, abdominal distention and ascites. The diet was restricted to fats and carbohydrates. Oral fluids were supplemented by approximately 300 cc. of one-sixth molar lactate per day. However, the patient continued to deteriorate. Coma and uremic frost appeared on May 11th. All other available measures having been exhausted, on May 11th treatment with the artificial kidney was started and continued for four hours. Calcium gluconate, 10 cc. of 10 per cent solution, was given intravenously at hourly intervals. During the treatment the blood pressure ranged from 130 to 170 mm. Hg systolic and 60 to 70 mm. diastolic. A febrile reaction to 104°F. occurred after one hour and was ascribed to the heparin and pyrogens in the tubing. The patient roused somewhat and the chest was free of rales after two hours. He was able to ask for fluid. The twitchings gradually diminished. However, the excoriations about the face began to ooze blood and at 1 A.M. on May 12th the treatment was stopped. A total of 820 mg. of heparin had been given intravenously during the treatment. Blood samples drawn from the patient failed to clot during the four hours of treatment. When the oozing of blood started, 500 cc. of fresh whole blood was slowly administered through the side circulation (Fig. 2) of the artificial kidney. The patient left the treatment room not appreciably altered clinically from the time of the onset of therapy.

At 6:45 A.M., 275 cc. of urine was found in the drainage bottle. The bleeding had stopped. The clotting time had reverted to normal. The blood pressure was 154 systolic and 68 diastolic. However, the patient's coma deepened and he expired at 7:45 A.M.

Autopsy revealed acute hemorrhagic bronchopneumonia involving the right upper, middle and left upper lobes. Acute tracheobronchitis

and pulmonary edema were present. Small hemorrhagic foci were found in the bladder, ureters, pelvis, kidneys, stomach, vocal cords, right epididymis, and around skin needle-puncture sites. Fibro-adenomatous hyperplasia of the prostate was marked.

The kidneys were enlarged, weighing 485 Gm. together. Fine punctate hemorrhages studded the surface. The surfaces of section were hyperemic; the corticomedullary demarcation was distinct. The glomeruli were visible as pale dots against an edematous background of cortex. The medulla was congested. Microscopic examination revealed congested and ischemic glomeruli frequently containing albuminous debris in Bowman's space. The proximal convoluted tubules showed mild degenerative changes. The distal convoluted tubules and collecting tubules were severely inflamed and contained zones of atrophy, necrosis and regeneration. The lumina contained eosinophilic, homogeneous and granular casts. The interstitium was focally infiltrated with chronic inflammatory cells. The intertubular capillaries were markedly congested. Several veins in the cortex were thrombosed.

The brain revealed discrete foci of hemorrhage and encephalomalacia, most marked on the lateral surface of the right temporal lobe. Microscopically, there was evidence of marked stasis and increased vascular permeability.

Comment. This was our first experience with the artificial kidney. The anuria was ascribed to cystoscopy, ureteral catheterization and sulfadiazine. The artificial kidney was used only after all hope for recovery had been exhausted. Urine (275 cc.) was voided in the six hours prior to death. At the present time we realize that treatment should not be deferred until irreversible changes have occurred. Moreover, if treatment with the artificial kidney is contemplated, surgical manipulation and creation of potential sites of bleeding should be avoided. The excoriations about the face and mouth were presumably due to pressure of oxygen masks and nasal catheters. These sites bled following heparinization. At autopsy small hemorrhages were found in the kidneys, bladder, pelvis, ureters, stomach and vocal cords. These areas had been the site of manipulation by either catheters

or Levine tubes. A hemorrhagic bronchopneumonia was present. Small foci of hemorrhage were found in the brain. It was recognized that the doses of heparin recommended by Kolff were far in excess of the amount required to prevent coagulation

TABLE V
BLOOD UREA NITROGEN AND SERUM CHLORIDES DURING
TREATMENT WITH ARTIFICIAL KIDNEY

CASE III: Chemical analyses of the blood during treatment with the artificial kidney. A, indicates the blood as it entered the machine from the radial artery; B, as it left the machine following dialysis prior to entry into a brachial vein. The water in bath at the end of four hours contained 27 Gm. of urea nitrogen.

	Urea Nitrogen (mg. %)	Chlorides (mg. %)	CO ₂ Content (vol. %)
1 ¼ hours { A.	244	515	38.2
{ B.	13	655	35.1
2 ½ hours { A.	232	538	37.4
{ B.	27	644	24.2
3 ¾ hours { A.	226	550	34.4
{ B.	13	642	21.5

during the passage of blood through the artificial kidney. This discrepancy between the recommended and required dose of heparin is perhaps explained by the lower potency of the heparin available to Kolff.

Urea nitrogen (27 Gm.) was removed from the blood in four hours and marked differences were noted in the urea nitrogen content of blood entering and leaving the machine. (Table v.) The carbon dioxide content of the patient's serum fell slightly during treatment. The carbon dioxide content of the blood leaving the artificial kidney was much lower than that of the blood entering the machine. This effect was believed due to the escape of carbon dioxide in the process of dialysis. Unfortunately carbon dioxide combining power of the serum was not determined. The carbon dioxide content of the original bath fluid was 53 volumes per cent; the final content was 49.4 volumes per cent. Serum chlorides increased gradually to a normal level. The bath fluid contained 749 mg. per cent of chlorides (as sodium chloride) at the end

of the run; the original bath fluid had contained 674 mg. per cent. This alteration in bath fluid can be explained by a decrease in volume due to evaporation.

CASE IV. E. G., a thirty-three year old woman in June, 1947 inserted two tablets of potassium permanganate into the vagina in order to induce an abortion. On July 5th, her menses failing to appear, she inserted two additional tablets. On the following day profuse vaginal bleeding began; she had shaking chills and a fever of 106°F. A physician administered one injection of 100,000 units of penicillin subcutaneously. In the subsequent twelve hours the patient also ingested 5 Gm. of sulfadiazine and 1½ Gm. of sodium bicarbonate. The chills and fever persisted and she was admitted to another hospital on July 7th. Physical examination revealed scleral icterus, slight tenderness in the right upper quadrant and vaginal bleeding. The hemogram revealed 3.75 million red blood cells, 22,500 white blood cells with 89 per cent polymorphonuclear leukocytes. Urine obtained by catheter contained bile, many red blood cells and a trace of albumin. The icterus and choloria disappeared several days after admission. On July 8th membranes which protruded from the cervical os were removed. She was treated with penicillin intramuscularly for the septic abortion and the temperature rapidly returned to normal. Oliguria was noted in the twenty-four hours following admission. On July 10th her blood urea nitrogen was found to be 150 mg. per cent.

On July 12, 1947, cystoscopy was performed. A few drops of clear urine were obtained from each ureter. The catheters were left in place for forty-eight hours but no urine was obtained. The patient became drowsy, nauseated and extremely thirsty. She was treated with intravenous sodium chloride, sodium lactate, Ringer's solution, sodium bicarbonate and a high colonic slow drip of 10 per cent magnesium sulfate. However, she failed to respond to these measures and on July 18th, following a transfusion of 250 cc. of whole blood, she was transferred to the Mount Sinai Hospital. At this time her blood urea nitrogen was 245 mg. per cent, creatinine 8.5 mg. per cent and the carbon dioxide combining power was 17 volumes per cent. Icterus index was 11, the van den Bergh test was negative, total proteins were 5.1 Gm. per cent (with a normal albumin-globulin ratio)

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and cholesterol was 124 mg. per cent (with 55 per cent esters).

Physical examination on July 18th revealed the presence of dyspnea, orthopnea, tachypnea and Kussmaul breathing. Twitchings were conspicuous. The temperature was 99.6°F.; pulse 120 per minute; respirations 40 per minute. The blood pressure was 140 mm. Hg systolic and 70 diastolic. There was moderate edema of the abdominal wall and back. Fine and coarse moist rales were heard at both lung bases. The abdomen was somewhat distended. Shifting dullness was present. No viscera were palpable in the abdomen. The remainder of the examination was within normal limits.

Laboratory studies on admission revealed a hemoglobin of 5.4 Gm.; 1.72 million red blood cells; 17,500 white blood cells, of which 87 per cent were segmented polymorphonuclear leukocytes, 4 per cent non-segmented and 6 per cent lymphocytes. Urine, 30 cc., were voided in the initial twenty-four hours following admission. The specific gravity was 1.010. The urine was straw-colored, cloudy, the pH was 7.0. It contained moderate amounts of albumin and many white blood cells and red blood cells on microscopic examination. The urinary chlorides were 621 mg. per cent; the urea nitrogen of urine 310 mg. per cent. The blood urea nitrogen was 145, uric acid 18.7 and creatinine 15.9 mg. per cent. The carbon dioxide content was 12.1 volumes per cent. The primary cause of the oliguria was not clear. Administration of sulfadiazine and cystoscopy seemed to be possible aggravating factors. The patient was given supportive therapy with digitalis, small transfusions of whole blood and oral and intravenous sodium bicarbonate. A necrotic placental mass was removed a few hours after admission.

On July 19th, although the patient appeared comatose and virtually moribund, the artificial kidney was applied. Heparin, 450 mg., was administered slowly through the venous cannula in divided doses. An hour after the cannula had been introduced a chill occurred and the temperature rose to 103°F.; this gradually subsided. Throughout the run there was no sign of improvement. At the end of one one-half hours the blood pressure gradually began to fall. The run was immediately terminated and 750 cc. of whole blood was given through the collateral inlet of the artificial kidney. Ten minutes after the treatment was terminated she again had rigors and twitchings which did

not respond to intravenous calcium gluconate. She remained in a coma and in peripheral collapse. The blood pressure was not measurable and the ventricular rate was 160 per minute with a tic-tac rhythm. No focal neurologic signs were obtained. The next morning she was unresponsive but had voided 2 ounces of urine. The lungs were clear. The clotting time was normal. The blood urea nitrogen was 195 mg. per cent, uric acid 19.1 mg. per cent, chlorides 580 mg. per cent, total protein 6.9 Gm. per cent and carbon dioxide content 10.7 volumes per cent. In the twenty-four hours following dialysis she voided 100 cc. of grossly bloody urine. Her blood pressure gradually returned to 110 systolic and 40 diastolic. Her downhill course continued and she expired on July 21st, fourteen days after oliguria was first noted.

Postmortem examination revealed no evidence of hemorrhage. The kidneys revealed the gross picture of lower nephron nephrosis. Their combined weight was 680 Gm. They appeared firm and tense. The exposed surface was dark gray and stippled. The cut surface revealed indistinct corticomedullary demarcation. The cortex was pale and edematous; the medulla revealed exaggerated black-gray rays converging in each papilla. The brain was edematous. Microscopic examination of the kidneys confirmed the gross impression.²²

Comment. The patient was transferred to this hospital in terminal uremia, severe heart failure and marked acidosis. Urine (30 cc.) were voided prior to her treatment with the artificial kidney and 60 cc. were voided following treatment. The chills and fever shortly after the start of dialysis were believed to be due to the heparin or pyrogens in the tubing despite scrupulous preparation. The fall in blood pressure made continuation of the treatment impossible since circulation through the machine could not be continued. At the end of the two-hour treatment with the artificial kidney 14 Gm. of urea nitrogen were found in the bath fluid. Other determinations were not attempted due to the unsatisfactory condition of the patient.

CASE V. J. W., a fifty-six year old white male, was admitted to the hospital on July 3, 1947, because of rectal bleeding which occurred with

each bowel movement. Control of the anal sphincter had been lost seventeen years prior to admission following surgery for a rectal abscess. Slight anorexia and a 12-pound weight loss had been noted during the six months prior to admission. The remainder of the patient's personal and family history was non-contributory.

Physical examination revealed a well developed, well nourished, chronically ill man. Temperature was 99°F.; pulse, 75; respirations, 14. The blood pressure was 145 systolic and 70 diastolic mm. Hg. The significant physical abnormalities were confined to the rectum which revealed the scars of previous surgical operations, a lax sphincter tone and a sessile fungating mass on the anterior and right lateral walls of the rectum.

Hemoglobin on admission was 13.0 Gm. The blood count and urinalysis were normal. The blood group was O (Landsteiner).

On July 7, 1947, an abdominoperineal resection was performed for adenocarcinoma of the rectum. The extension of the carcinoma into adjacent structures rendered its removal difficult. Bleeding was profuse and the blood pressure fell to 55 systolic and 30 diastolic. Despite administration of 2,000 cc. of whole blood the blood pressure remained at 75 systolic and 50 diastolic. A chill occurred following administration of the third 500 cc. of whole blood. Investigation revealed that 500 cc. of group A (Landsteiner) blood had been given. Following the subsequent administration of 2,500 cc. of whole blood, 500 cc. of saline and 600 cc. of one-sixth molar sodium lactate solution intravenously, the blood pressure gradually rose to 124 systolic and 69 diastolic. The marked fall in blood pressure had persisted for approximately eight hours.

The subsequent course of the patient, urinary output, blood and urine examinations are illustrated in Table VI. On July 8th, the morning following the operation, the blood pressure was 130 systolic and 70 diastolic. The patient was drowsy, responded poorly but was coherent. The total volume of intravenous and oral fluid was limited to a slow replacement of the amount obtained by Wangenstein suction plus 1,000 cc. for insensible loss. The choice of isotonic sodium chloride, 5 per cent glucose or one-sixth molar lactate was determined by the carbon dioxide and chloride content of the blood. Only 15 cc. bloody urine were voided during the twelve hours following operation. Successive specimens

of urine were found to contain large amounts of albumin, many epithelial cells, 6 to 10 red blood cells and a few to many white blood cells per high power field. The specific gravity of casual specimens ranged from 1.014 to 1.019. The hemoglobin was 10.4 Gm. On July 10th the

TABLE VI

CASE V: Course prior to and following treatment with the artificial kidney.

July	Urine		Blood			Blood Pressure
	Vol./24 hr.	Urea Nitrogen (mg. %)	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Carbon Dioxide Content (vol. %)	
5	9	145/70
8	15 cc.	...	33	54.5	55/30
9	47 cc.	50	50	4.6	60.5	130/70
10	60 cc.	72	68	5.9	57.0	136/80
11	80 cc.	125	81	6.6	42.4	136/78
12	80 cc.	150	125	7.5	47.0	136/76
13	250 cc.	...	120	61.0	154/70
14	200 cc.	175	147	9.2	184/84
15	200 cc.	163	183	10.5	51.0	172/84
16	275 cc.	388	142	10.1	37.0	180/80
17*	250 cc.	330	95	11.9	41.0	176/84
18	475 cc.	260	107	14.3	50.0	110/70
19	725 cc.	160/64
						130/70

* Chemical values on July 17th were determined on blood drawn nine hours after artificial kidney was disconnected.

patient was alert and cooperative. Dependent edema and basal pulmonary rales appeared which promptly responded to further fluid restriction and digitalization. On July 13th the colostomy functioned well. On July 15th twitchings appeared and the patient appeared somnolent. Occasional, moist, bilateral, basal rales were heard. On July 16th he could not be roused. Twitching and hypersensitivity to mild stimuli were marked. The lungs were full of coarse, moist rales. All observers agreed that the patient was *in extremis*. It was thought that all other available measures had been exhausted and that the artificial kidney could certainly do no harm.

The patient was treated with the artificial kidney on July 16th for eight hours. Heparin (700 mg.) was given intravenously over the initial two-hour period. Serial studies of the clotting time failed to reveal any evidence of clotting during the eight hours. The blood pressure was well maintained during this entire period. Restlessness and twitchings became less marked and after two hours the patient responded to his name. At the end of the dialysis

the pulmonary edema was no longer present. Following this marked improvement, the patient slowly became semicomatose once more. Perineal oozing of blood was noted after six hours. Whole blood (1,000 cc.) was then administered slowly, by-passing the machine. At the end of the dialysis an estimated 500 cc. of the patient's blood was deliberately left in the machine to prevent overloading of his circulation. One hour after completion of the dialysis the oozing stopped. The details of alterations in the patient's blood and the contents of the bath fluid following dialysis are included in Table VII.

The blood urea nitrogen had risen from 9 mg. per cent on July 7th to 142 mg. per cent on July 16th immediately prior to application of the artificial kidney. After eight hours of dialysis the urea nitrogen level had fallen to 92 mg. per cent. However, the level again rose in the ensuing days. This rise is ascribed to persistent oliguria, impaired concentrating capacity of the kidneys, continued endogenous production of urea nitrogen, and re-equilibration of the dialyzed circulating blood with the tissue fluids. Similarly, in the nine days prior to dialysis the serum creatinine rose from 2.9 mg. per cent to 5.8 mg. per cent. Following dialysis the blood level fell to 4.7 mg. per cent but three days later had again climbed to 11.2 mg. per cent. During the eight hours of treatment the serum chlorides increased slightly. The total proteins were not significantly altered. Slight hemolysis was indicated by the gradual increase in icterus index. Changes in blood constituents during and following dialysis are indicated in Tables II and III. No change in blood volume was demonstrated prior to or after the run (Evans blue).

The morning after treatment, July 17th, the patient was restless and disoriented. There was marked sweating, twitching and cyanosis. The lungs were clear. The blood pressure was 110 systolic and 70 diastolic. On July 18th nuchal rigidity appeared. Lumbar puncture yielded bloody, xanthochromic fluid. No microorganisms were found on smear or culture. Total protein and chlorides were normal. The blood pressure was 160 systolic and 64 diastolic. On July 20th bilateral, constant Babinski reflexes and Cheyne-Stokes respiration were observed and the patient died.

Postmortem examination revealed severe pulmonary edema, congestion and broncho-

pneumonia. Both cardiac ventricles were dilated. Multiple, small focal ecchymoses were found in the renal pelvis and bladder mucosa.

The kidneys grossly presented the picture of hemoglobinuric nephrosis. Microscopic examination revealed normal-appearing glomeruli

had gradually increased to 275 cc. in the twenty-four hours prior to dialysis.

Analytic data obtained during dialysis are given in Table VII. The blood urea nitrogen, creatinine and uric acid fell steadily during dialysis; the concentration

TABLE VII
CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH ARTIFICIAL KIDNEY

CASE II: Upper chart: Blood chemistries before and after dialysis. The dialysis decreased in efficiency because the bath water was not changed during the entire eight-hour run. Lower chart: Bath water samples taken at two-hour intervals indicate gradual increase of dialyzed products. Total bath fluid is 100 L. Consequently, in eight hours 59 Gm. of urea nitrogen, 2.5 Gm. of creatinine and 2.9 Gm. of uric acid had been removed from the blood.

	Urea Nitrogen (mg. %)	Creatinine (mg. %)	Uric Acid (mg. %)	Phosphorus (mg. %)	CO ₂ Content (vol. %)	Chlorides (NaCl) (mg. %)	Icterus Index	Total Proteins (Gm. %)
Control*	142	5.8	10.1	3.0	468	12	5.0
2 hours { A.	141	5.9	9.8	2.0	30.5	515	12	4.8
{ B.	53	3.8	6.6	1.2	27.0	538	15	4.7
4 hours { A.	112	5.1	10.1	2.0	30.0	527	15	4.3
{ B.	40	2.6	4.9	2.1	31.0	573	21	4.3
6 hours { A.	87	5.1	8.6	2.0	26.0	573	15	4.4
{ B.	56	3.1	5.6	1.6	26.3	632	21	3.7
8 hours { A.	92	4.7	7.2	2.0	28.0	620	20	4.6
{ B.	52	2.8	4.9	1.5	25.6	550	20	4.6

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Creatinine	Uric Acid	Phosphorus
2 hours	17	1.2	...	1.6
4 hours	36	1.6	1.8	1.5
6 hours	56	2.1	2.4	2.0
8 hours	59	2.5	2.9	2.0

* Control chemistries were drawn six hours prior to treatment with artificial kidney.

A. = Blood sample from radial artery en route to machine.

B. = Blood sample following dialysis from machine to brachial vein.

except for albuminous material in Bowman's space. The severest degenerative changes were found in the loops of Henle and distal convoluted tubules which contained hemoglobin casts. Areas of necrosis and regenerating tubular epithelium were present. The cortex and medulla showed focal infiltration with chronic inflammatory cells. The blood vessels were congested with few antemortem thrombi.

Examination of the brain was not made.

Comment. The artificial kidney was applied after nine days of oliguria and progressive uremia. The urinary output

of these retention products in the bath fluid increased concomitantly. The carbon dioxide content of the serum diminished slightly; serum chlorides gradually rose. There was little change in the total protein of the serum; the protein content of the bath was not determined. A slight degree of hemolysis was indicated by the increase in icterus index of the serum during dialysis. Although the level of serum phosphorus remained unchanged, appreciable quantities appeared in the bath fluid. The plasma glucose level of blood obtained from the

radial artery rose from 80 mg. per cent prior to treatment to 280 mg. per cent at the end of treatment.

The downhill course of the patient continued following dialysis. However, the urinary output continued to increase. The day following treatment with the artificial kidney signs of meningeal irritation appeared. Xanthochromic fluid containing many red cells were obtained by lumbar puncture. The bleeding was ascribed to either heparin and/or uremia. Of interest in this regard is the concept of Globus²³ that cerebral softening antecedes cerebral bleeding. This patient, fifty-six years of age, and B. C., sixty-two years of age, manifested intracranial bleeding. When loss of vascular structure or support has occurred, potentiation of hemorrhage by heparin may be anticipated. Jorpes has stressed the large doses of heparin that may be administered to animals and man without producing hemorrhage as long as vessel walls remain intact. Consequently, heparinization appears less hazardous in younger age groups.

It is our impression that restitution of kidney function might have been accomplished in this patient had we started to use the artificial kidney sooner. In addition smaller doses of heparin appear to be indicated, especially in older patients in whom degenerative vascular changes may have occurred.

CASE VI. L. M. was transferred to the Mount Sinai Hospital in November, 1947, because of anuria and marked oliguria of five days' duration. His past history included an appendectomy in 1943 and myocardial infarction in 1944. Chronic cholecystitis and cholelithiasis were known to be present since 1945. The patient was admitted to another hospital where cholecystectomy was performed and a gallbladder full of stones was removed. The operation was uneventful and the blood pressure was well maintained. On the first postoperative day the patient's condition was satisfactory and he voided 400 cc. of urine. On the second postoperative day he suddenly developed a fever of 106.6°F. followed by a precipitous fall in blood pressure to 76 mm. Hg systolic. The blood

pressure hovered around that level for the next forty-eight hours. No urine was voided during the second and third postoperative days. After forty-eight hours of shock the blood pressure gradually rose to a high of 172 systolic and 95 diastolic. There was no subsequent fall. No urine was voided except for approximately 30 cc. per day on the fourth and fifth postoperative days. The abdomen remained soft; the wound was examined and probed, but no abnormality was noted. Blood cultures were negative. A right lower lobe pneumonia was treated with penicillin. As the anuria persisted the blood urea nitrogen rose to 114 mg. per cent. No urine could be obtained from either renal pelvis by cystoscopy and ureteral catheterization. After five days of anuria the patient was transferred to the Mount Sinai Hospital for treatment with the artificial kidney.

Physical examination revealed an acutely ill, somnolent and somewhat disoriented male. His skin itched. He had constant muscular twitching and Cheyne-Stokes respiration. The temperature was 101°F. The blood pressure was 172 mm. Hg systolic and 95 mm. diastolic. There was no jaundice or peripheral edema. The mouth and tongue were dry. Examination of the lungs revealed coarse rales over the right lower lobe posteriorly, with impaired percussion note over the same area. The lungs were otherwise normal. The heart was normal. The pulse was regular and slow. The abdomen was distended and audible hyperperistalsis was noted. There was a healing upper abdominal incision with retention sutures and drains in the upper angle of the wound. There was no pus on probing of the wound and no wound tenderness. There were no palpable abdominal masses.

Examination of the blood revealed a hemoglobin of 13.8 Gm., white blood count 14,300 with 81 per cent segmented polymorphonuclears, 12 per cent stab cells and 4 per cent lymphocytes. The patient was catheterized on admission and 6 cc. of very bloody urine were obtained. Urinalysis showed a specific gravity of 1.020, protein 3 plus, many casts, leukocytes and red cells. The blood urea nitrogen was 110 mg. per cent on the night of admission and 124 mg. per cent on the following morning. The carbon dioxide content of the blood was 49.1 volumes per cent. The electrocardiogram showed no evidence of recent myocardial infarction. It was believed that the patient had a hepatorenal syndrome following cholecystectomy.

The restlessness, twitchings, convulsive movements and cerebral depression continued to progress. On the morning after admission treatment with the artificial kidney was begun. Heparin (400 mg.) was given intravenously in divided doses prior to the onset of dialysis. Repeated tests of the clotting time failed to show any evidence of clotting within four hours. After one hour of dialysis bleeding developed at the operative site. The oozing persisted and after the second hour of dialysis the blood pressure gradually fell to a level of 90 systolic and 60 diastolic. With the drop in systolic blood pressure, the circulation through the apparatus could not be maintained and dialysis had to be terminated. Three units (1,500 cc.) of whole blood and 6 cc. of 1 per cent protamine sulfate had been given via the collateral inlet of the artificial kidney; two additional units of whole blood were subsequently administered in the next hour. The clotting time reverted to 7 minutes, the oozing stopped and the blood pressure rose to 110 systolic and 70 diastolic within an hour after dialysis was terminated.

Immediately before the start of dialysis the following data were obtained: blood urea nitrogen 107, uric acid 16.7 and creatinine 10.5 mg. per cent. At the end of two hours of dialysis the blood urea nitrogen had fallen to 69, the uric acid to 7.1 and the creatinine to 7.2 mg. per cent. The 100 L. of bath fluid were found to contain 20 mg. per cent of urea nitrogen, 4.8 mg. per cent of uric acid and 2.9 mg. per cent of creatinine. Following dialysis, as the interstitial fluids and the circulating blood once again equilibrated, the blood content of these substances rose again. The blood urea nitrogen determined daily increased steadily to 103, 112, 132 and finally 154 mg. per cent. The carbon dioxide content of the blood gradually dropped to 39.4 volumes per cent.

The morning after dialysis 90 cc. of grossly bloody urine were obtained by catheter. During the next few days the urinary output gradually increased so that twenty-four hours prior to death the patient voided 250 cc. The specific gravity ranged from 1.014 to 1.020. The urine contained albumin, many red, white and epithelial cells and moderate numbers of granular casts. The manifestations of uremia were progressive. The temperature rose to 105°F. and the patient expired on the sixth hospital day.

Postmortem examination revealed acute pulmonary edema. The right coronary artery was found to be the site of an old thrombotic oc-

clusion with resultant infarction of the posterolateral wall of the left ventricle. The right hepatic artery had been ligated surgically and two peripheral infarcts of the liver were present. The kidneys together weighed 560 Gm. and revealed bilateral, subacute cortical necrosis with secondary inflammation and pyelitis. On microscopic examination the entire renal cortex showed severe degeneration and necrosis of the epithelium of the convoluted tubules. The intervening stroma was edematous and infiltrated by lymphocytes and large mononuclear cells. The renal alterations were ascribed predominantly to shock; the influence of ligation of the hepatic artery could not be evaluated.

Comment. This patient had been in chronic shock possibly initiated or aggravated by ligation of a main hepatic artery and consequent focal infarction of the liver. He was in far advanced uremia at the time that therapy with the artificial kidney was instituted. Shortly after large doses of heparin were administered oozing at the operative site was noted. The wound had been repeatedly probed and manipulated by surgeons who were attempting to find a local cause for the fever. It is questionable whether the wound would have bled seven days after operation had these manipulations not occurred. The bleeding led to a fall in blood pressure despite administration of whole blood by the collateral inlet of the artificial kidney. As the blood pressure fell circulation through the kidney became ineffective and stasis occurred in the loops. A controlled volume of blood was returned to the patient and treatment was terminated.

The possibility of shock due to exsanguination of the patient into the machine is counterbalanced by filling the cellulose acetate coils with either blood or saline prior to the start of dialysis. Consequently as blood enters the apparatus displaced blood or saline is returned to the patient. Even a slight excess of inflow over egress causes distention of the tightly wound coils and permits immediate reduction in the volume of blood leaving the patient while return to the patient continues unabated.

The dialysis in this instance was limited to two hours. However, marked diminution

in blood urea nitrogen, creatinine and uric acid were demonstrated even in this short time, illustrating again the dialyzing efficiency of the apparatus.

COMMENTS

We have treated six patients with the artificial kidney; case II was treated twice. Cases I and II are our recent patients; both recovered. Cases III, IV, V and VI constitute the initial group treated with the artificial kidney. They were *in extremis* prior to treatment. However, they served to establish the potentialities of the apparatus and to indicate the advisability of applying the artificial kidney before irreversible changes have occurred.

There can be no doubt that the Kolff artificial kidney is mechanically capable of efficient and rapid dialysis. The exposure of a large surface of blood to a bath fluid of predetermined composition is accomplished by means of the semipermeable membrane of cellulose acetate. Small molecules (up to a molecular weight of approximately 35,000) traverse this membrane. The rate of molecular exchange across the membranes is largely influenced by the relative concentrations of the solutes in blood and bath as well as the duration of exposure of the blood film to the bath fluid. The dialysis is controlled by variation in the composition of the bath. Urea, creatinine, uric acid, sodium, calcium, phosphorus, phenols and substances of similar molecular weight are readily removed; the larger molecules, including the serum proteins, traverse the membrane with difficulty. Any substance in blood capable of freely passing through the membrane may be removed from the blood by omitting it from the bath fluid.

Other types of "artificial kidneys" have been built. The essential principles are similar in all. The variations depend upon the mechanical ingenuity of the creator. However, all types require the use of heparin to maintain the fluidity of the blood as it passes through loops of cellophane; heparin has made the artificial kidney possible. However, its shortcomings

must be kept in mind. Recent surgical operation or other trauma creates the hazard of bleeding due to heparinization. Large doses of heparin had been advocated to prevent coagulation in the apparatus.¹² We soon learned that this dosage is excessive. Our first patient (Case II), a sixty-three year old male, was given 820 mg. of heparin in four hours. Postmortem examination revealed small hemorrhagic foci in the brain. A fifty-six year old male (Case III) was given 700 mg. of heparin intravenously over an eight-hour period. Permission to examine the brain at autopsy was denied. However, xanthochromic fluid was obtained by lumbar puncture. The predisposition of these older patients with uremia to hemorrhage is well known and caution in heparinization is essential. A young woman (Case III) was given 450 mg. intravenously in one hour. At autopsy she showed no evidence of intracranial bleeding. No significant visceral hemorrhage was found in any case. We now use 100 to 200 mg. of heparin intravenously at the start of dialysis, followed by 50 to 100 mg. intravenously as determined by hourly determinations of the clotting time. A coagulation time of at least one to two hours during the treatment appears desirable. Whole blood, toluidine blue and protamin are available at all times as heparin-antagonists.

The literature contains descriptions of various methods of dialysis. These include perfusion of intestinal loops, serous surfaces and synthetic membranes. It is not the purpose of this paper to evaluate the relative merits of these methods. The end sought by each means is identical. However, use of an apparatus which permits dialysis outside of the body is more benign than other measures which either require major surgical intervention or have the obvious hazard of causing infection. Even the use of a Miller-Abbott tube and continued irrigation of the intact intestine¹¹ is a tedious and troublesome process usually complicated by diarrhea which further disturbs water and electrolyte balance.

It is our intention to employ the artificial

kidney in those patients with acute non-obstructive anuria who fail to respond to conservative, well directed medical management. Murray¹⁸ has noted the poor results obtained in animals which are allowed to become moribund prior to the onset of therapy. Our experiences also indicate that irreversible changes must not be permitted to occur before dialysis is undertaken. We have stressed elsewhere the relatively high incidence of spontaneous diuresis in acute non-obstructive nephropathies and have urged care in maintaining electrolyte balance and avoidance of circulatory embarrassment by over-zealous administration of fluid. When it becomes apparent that medical measures are failing, artificial dialysis should be considered. It is obvious that this treatment is not curative but can aid in prolonging the patient's life until spontaneous regeneration of the damaged renal tissue may occur. By the same token it is obvious that the artificial kidney should be reserved for those cases in which restoration of renal function can be anticipated rather than for cases of chronic progressive renal disease.

SUMMARY

The Kolff artificial kidney was used in six cases of acute uremia caused by non-obstructive nephropathies. Clinical histories and laboratory data are presented in detail. The apparatus was shown to be mechanically competent. Its sphere of usefulness is described.

Acknowledgments. During the course of these investigations the authors received assistance and guidance from friends and colleagues too numerous to mention individually. Special thanks are due to Drs. G. Baehr, I. Snapper, W. J. Kolff and S. Jarcho. Drs. M. Steinberg and J. Priver rendered administrative assistance. Dr. H. Sobotka and Miss M. Reiner supervised the many chemical analyses performed by their staff.

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Transperitoneal Lavage for Twenty-six Days in the Treatment of Azotemia*

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EVER since the introduction in 1914 by Abel, Rowntree and Turner¹ of the artificial means of removing substances ordinarily excreted by the kidney, considerable attention has been focused on newer and more satisfactory means of combating azotemia. It is a well known fact that when the blood concentration of non-protein nitrogen and urea is elevated these substances will be excreted into the intestinal tract. Advantage of this fact was taken by the use of gastroduodenal lavage and the production of diarrhea with only moderate success. Suggestions for the use of isolated loops of intestine subjected to continuous lavage seem for the moment doomed to failure since studies to date indicate that over 10 feet of bowel as an isolated segment would be required to supply 10 per cent of maximum normal renal clearance (75 ml. per minute). The procedure is at present still being studied by Kolff who hopes to succeed in this with the use of proper dialyzing fluids and diet. Ochsner has suggested that the employment of gastroduodenal lavage may be a solution to the problem. However, completed studies employing this method have not been reported. Kolff and Berk² have recently popularized the "vivi-diffusion" method in treatment of azotemia. This procedure involves the use of some 25 to 30 meters of cellophane-like material similar to sausage casing (which is a permeable membrane) submerged into a container filled with a salt solution that can be varied with the changing blood chemistry of the patient. In this manner the

blood proteins are preserved and acidosis and other acid-base factors can be more readily controlled. Blood is introduced into the unit from a cannulated artery and is allowed to trickle over the extensive surface area (20,000 sq. cm.) presented by the cellophane tubing. As the blood flows through the tubing, dialysis takes place and an equilibrium is established between the blood and the extratubular fluid. In this manner the nitrogenous products which are crystalloids are removed from the blood stream. The blood is then readmitted into the circulation by pumping it into a vein. Naturally, this procedure calls for having the patient well heparinized. This unit is very efficient but the technicalities involving the use of this procedure, construction and operation of the unit are responsible for its rather limited use and acceptance. Still other methods for treating azotemia are decapsulation,^{3,4} high splanchnic block⁵ and the use of large doses of heparin. The latter procedure is advocated by Kallner⁶ and shows promise in selected cases. Decapsulation is of unquestionable value when edema of the kidneys precludes their function because of compression of the renal parenchyma. Peritoneal lavage was introduced by Ganter in 1923⁷ and has been resorted to clinically on numerous occasions. At least twenty-two cases have been reported in the literature and eight recoveries can be attributed to its use.

The need for some temporary renal substitute occurs only when reversible or non-permanent damage or insult involves the

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kidneys. These occasions are those involving hemolytic crisis following the infusion of improperly typed blood, toxic sulfa reactions, mercurial poisoning, crush syndromes, burns and other forms of urinary tract disease in which the ultimate prognosis is fair if the immediate crisis can be met. Truetta⁸ has pointed out that renal anoxia, found in a number of pathologic conditions, was probably the result of overstimulation of the vascular nerves. He further showed that by peripheral reflex and direct stimulation the renal cortex of the kidney became completely ischemic. He concluded by noting that under such conditions the flow of urine is decreased or may be entirely suppressed. His implications are that "nerve stimulation could be produced centrally or peripherally by a variety of noxious agents and the picture seen in many loosely related syndromes—e.g., 'sulfa-kidney,' incompatible-transfusion kidney, Weil's disease, and some forms of nephritis—is the result of a defense device by which the cortex of the kidney is excluded from the circulating toxin or other noxious agents and thus protected." Too prolonged operation of the device results in permanent damage. This concept of a functional change-over under various conditions to a medullary renal circulation has obvious physiologic, pathologic and clinical implications. For instance, the interpretation of renal function tests must be considered. The pathology of hysterical uremia, emotional anuria, post-abortion and post-traumatic uremia, and the response of these last two to splanchnic block are readily explained. Olson and Necheles called attention to the controversy over the mechanism of impaired renal function.⁹ It was pointed out that a number of patients with peptic ulcer, who had normal renal function before treatment with calcium carbonate, developed marked depressed renal function during alkalosis. The Army Malaria Research Unit at Oxford¹⁰ described the effects of large doses of alkali in normal men and found that all subjects had disturbances of renal function. Baker and Dodds¹¹ theory of acidosis pre-

cipitating acid hematin with subsequent mechanical block in the tubules has been subjected to considerable criticism. This, of course, is the basis for the alkalosis therapy. Wakeman¹² states that there is no support for the theory that acidosis in blackwater fever is an indication for alkaline therapy. Foy and Kondi¹³ described cases of anuria frequently developing in patients who had slight hemolysis and passed alkaline urines and other patients who failed to develop anuria although they had marked hemolysis with an acid urine. In 1943 these workers¹⁴ carefully reviewed the alkalinization hypothesis and concluded that there was insufficient evidence to warrant any statement as to the efficiency of alkaline solutions in either preventing or relieving the oliguria and anuria in blackwater fever, incompatible transfusions and crush injuries. However, the institution of the alkaline therapy very early in hemolytic accidents before oliguria or anuria become apparent may be the reason for its so-called success in many cases. The same may hold true for the intravenous use of isotonic sodium sulfate as described by Olson and Necheles.⁹ At any rate, it is evident that considerable confusion exists in the understanding and treatment of oliguria and anuria whether it be from the more common sequelae or from other more remote complications.

Transperitoneal lavage has been studied very carefully by a number of investigators.^{15,16,17} Fine, Frank and Seligman^{18,19,20} have been pioneers in this procedure and have reported their results elsewhere. Ganter's original work in 1923 has been improved upon by these authors with the institution of continuous lavage and the use of lavage fluid more closely resembling the electrolyte composition of extracellular fluid. The lavage fluid must be considered carefully insofar as the blood chemistry of the patient can and will be altered by changing its composition. By making the fluid hypo- or hypertonic, the blood stream and hence the extracellular fluid will react in the usual manner. Generalized edema and especially pulmonary edema can thus

be regulated and controlled by it. The composition of the lavage fluid as suggested by Seligman *et al.*²⁰ is a modified Tyrode's solution. It is reputed to be especially effective in combating acidosis, but that this does not hold will be illustrated by the

thus accomplish dehydration. Dehydration can be still further increased by eliminating all sodium salts from the lavage fluid.

The apparatus used in the case reported here follows that of Fine *et al.* very closely. Several minor variations were introduced

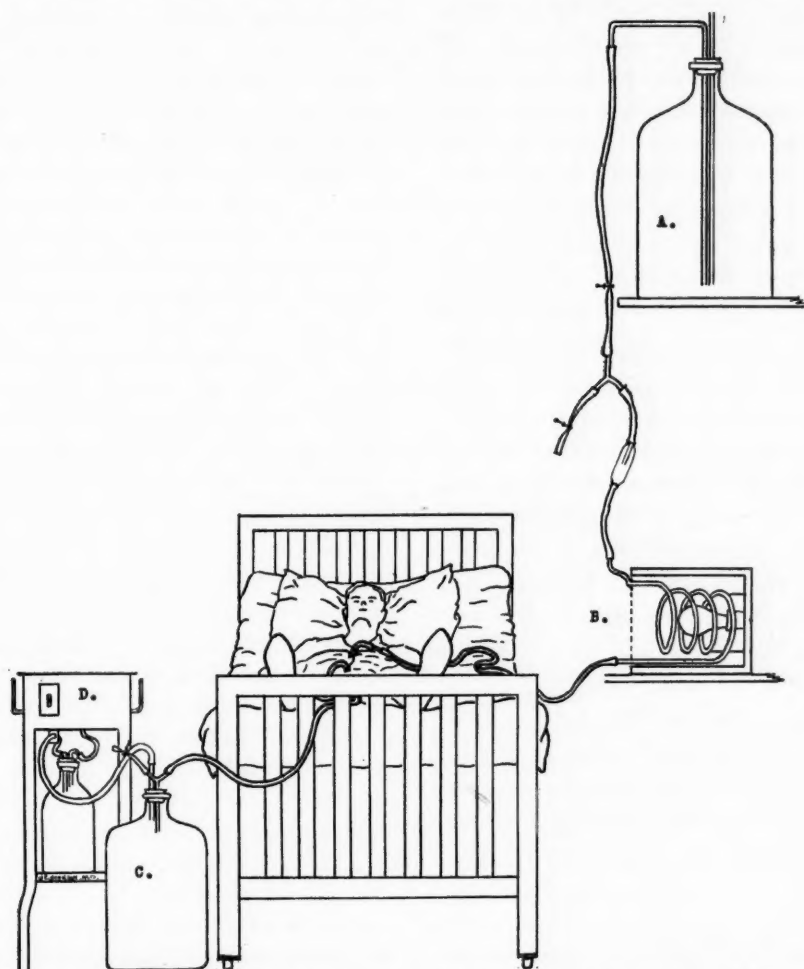


FIG. 1. This illustrates the simplicity of the apparatus used in transperitoneal lavage. A is the constant head siphon storing the influent lavage fluid; B shows the details of the heating unit used to bring the lavage fluid to body temperature; C is the effluent lavage fluid container; D is the suction pump.

case we are reporting. Slight alterations of the composition of this fluid, as by the addition of greater amounts of glucose, will provide nearly all of the caloric requirements of the patient and hence eliminate the necessity of parenteral administration of fluids of this sort and thus limit the possibility of pulmonary edema. Should pulmonary or generalized edema develop the fluid can be made hypertonic with 5 per cent gelatin and 2.5 per cent glucose and

which we believe were of value. One of these was the method used in bringing the lavage fluid to body temperature. This consisted of a small wooden box, measuring about 1 cu. ft., in which was mounted a lamp socket and lamp. About 4 feet of $\frac{3}{8}$ in. copper tubing was coiled closely around the lamp. It was found that a lamp of about sixty watts was sufficient to raise the temperature of the lavage fluid from room to body temperature. This procedure con-

served approximately 500 calories of body heat per day as well as provided a more homeostatic character to the lavage fluid. Once the lavage fluid was started the temperature adjustment required no further attention. The heating unit could be conveniently placed in bed with the patient. Another variation was the introduction of a constant head siphon in the lavage fluid storage bottle. This provided a constant flow to the fluid and once set need not be changed or adjusted. A number of different types of suction pumps was used to remove the lavage fluid from the peritoneal cavity, but the one thought to be most satisfactory was the Thermotic Drainage Pump.* This pump provided ample suction without danger of trauma to the viscera and also had the added feature of being entirely noiseless. The lavage fluid was prepared in ordinary 5 gallon carboy bottles and mounted on a platform stepladder about 3 feet above the patient. The bottles were sterilized before each batch of lavage fluid was prepared by inserting them into the dressing room steam sterilizer on the ward floor. They were filled with freshly distilled water without any further efforts to sterilize the water. Tyrode's solution was prepared in accordance with the suggestions of Fine *et al.* and added to the distilled water. Figure 1 illustrates the equipment used by us.

CASE REPORT

On March 7, 1947, C. H., a thirty-one year old colored male, was admitted to St. Luke's Hospital, Chicago, in a confused state following two convulsive seizures. His wife who accompanied the patient left before any history could be elicited. The patient was irrational to the extent that he did not know nor realize where he was, hence no history pertaining to his illness could be obtained from him. His blood pressure upon admission was 240 systolic and 140 diastolic, pulse 90 and temperature 99.2°F. rectally. Respirations were 25 per minute and labored. His chest had a few moist rales in both bases. The liver was 3 cm. below the costal

* Manufactured by the Gomco Surgical Manufacturing Company.

margin. There were no neurologic findings. Venesection was performed and aminophyllin and sedation given. The usual emergency laboratory tests were negative and the impression was that of a hypertensive encephalopathy.

The following day additional history was obtained from his wife. She stated that the patient had been quite well except for a cold from which he had recovered. She added that he was a known hypertensive but had been without symptoms until three days preceding his admission. On the day of admission he awoke complaining of epigastric pain and nausea. He did not vomit. This continued and was unrelieved by a cathartic; the patient was taken to his own doctor who told him that he needed digitalis. That morning he took two tablets and a second similar dose at noon. About this time he complained of blurring of vision and some mental confusion. About 2 P.M. he had a convulsive seizure which his wife described as beginning with a cry and followed with a spastic type of condition immediately preceding a more dynamic type of convulsion. The description was that of a rather typical grand mal seizure. It had a duration of about two minutes or less. There was a second seizure an hour or so later and the patient was then brought to the hospital arriving about 5:00 P.M. The patient never had convulsive seizures in the past.

He was known to be hypertensive for the past four years. At this time he was employed at the Duke University Hospital. It was here that his hypertension was discovered. An operation was considered and then decided against. The patient had been on a low salt, low protein diet since that time. He had one or two episodes of ankle edema and became dyspneic with slight exertion. He did not complain of orthopnea, chest pain, cough or hemoptysis. To anyone's knowledge he did not have nephritis, but it was stated by his wife that all of his family died of so-called "heart dropsy." The patient was born and reared in North Carolina and left there eighteen months before his admittance to our hospital.

Inventory by systems revealed that the patient neither gained nor lost weight. His health was considered "precarious." He had had severe headaches on exertion ever since childhood. He had one very sore throat when a child which kept him in bed for two weeks. The gastrointestinal review was negative except for the pain and nausea described in the history and

constipation for which he used numerous laxatives. The genitourinary system was normal with the exception that the patient was bothered with frequency and nocturia. For this reason he avoided fluids after eating his evening meal.

His past history revealed that he had the usual childhood diseases. There was no history of nephritis or rheumatic fever, neither was there any history of surgery.

His personal history revealed that he was a butler, that he used tobacco only occasionally, did not use alcohol and that he remained constantly on a salt poor and low protein diet. His appetite was described as being poor.

Physical examination at this time revealed a well developed, well nourished colored male about thirty-one years of age lying quietly in bed somewhat confused and very somnolent. The external ocular movements were normal; pupils were round and equal but reacted sluggishly to light and accommodation. Funduscopic examination revealed a hypertensive retinitis grade 3. There were no new hemorrhages. The ears, nose, throat and neck were essentially normal. His lungs were now clear to percussion and auscultation and tactile fremitus was bilaterally equal. The heart sounds were markedly accentuated. The rhythm was regular and the rate was 100. The apex was found to be 2 cm. to the left of the mid-clavicular line. No murmurs were heard in any of the stations with the exception of some roughening of the first tone at the apex. There was no friction rub. The blood pressure at this time was 238 systolic and 112 diastolic. The liver, kidneys and spleen were not palpated. There was no abdominal tenderness or rigidity and no evidence of any mass in the abdominal cavity. The bowel sounds were normal. The bladder was not distended and there was no costovertebral tenderness. The genitalia were normal and there was no evidence of edema. Neurologically, the reflexes were bilaterally equal and physiologic. The cranial nerves were all intact and no pathologic reflexes were found.

The morning after admittance the patient remained in a semi-stuporous condition. He voided 400 cc. at noon and later the same day was catheterized to check for obstruction and 40 cc. of urine were obtained. The urethra was patent throughout. At 5:00 P.M. the same day he again voided 200 cc. Laboratory reports at this time showed a red blood count of 2,080,000; white blood count 14,900; hemoglobin 6.8 Gm.

per cent; non-protein nitrogen 150 mg. per cent; creatinine 11.9 mg. per cent; CO₂ combining power 54 volumes per cent; icteric index 2.0. His total urinary output for that day was 640 cc.

The following day he voided 100 cc. and none the following two days. An electrocardiogram indicated myocardial damage on a hypertensive basis. His blood chemistry now showed a rapid increase in nitrogenous products with his anuria and on the fifth hospital day had this picture: non-protein nitrogen 258 mg. per cent; urea 203 mg. per cent; creatinine 22.2 mg. per cent; total protein 5.6 Gm. per cent; calcium 9.6 mg. per cent; phosphorus 13.8 mg. per cent. In addition his red blood count had fallen to 1,080,000; white blood count was now 19,000 and hemoglobin 4.3 Gm. per cent. A differential white count showed 94 per cent polymorphonuclear leukocytes and 6 per cent lymphocytes. The urine voided on the second hospital day was acid in reaction and had a specific gravity of 1.008, 100 mg. per cent plus albumin, 2 plus red blood cells and 3 plus white blood cells. It was negative for sugar and showed occasional granular and hyaline casts.

Prior to this time the patient had already showed uremic frost and all of the other clinical signs of a full blown uremia. A portable KUB plate made on the second hospital day indicated a possibility of a renal stone in the left renal pelvis. It was very evident that the patient's condition was at the terminal stage. No specific diagnosis had been made up to this time. Several of the more obvious diagnoses were considered, among them polycystic kidneys and a malignant nephrosclerosis. Still it was believed that this could be a reflex anuria on the basis of a stone somewhere in the genitourinary tract. A renal stone in the presence of already damaged kidneys could explain the clinical picture presented by this patient. With the strong impression that the possibility of recovery was remote, the patient was subjected to continuous transperitoneal lavage in order to reduce his azotemia.

With the patient in bed and under local anesthesia two midline incisions were made. One, for the influent lavage tube, was placed mid-way between the xiphoid process and the umbilicus. The effluent side was placed approximately 4 cm. above the symphysis pubis. A better positioning of these tubes would have been to place them in either flank as shown by other investigators. The influent tube consisted of ordinary laboratory rubber tubing

$\frac{3}{8}$ in. in diameter with multiple perforations. The tubing was about 6 inches long. The effluent tube was a stainless steel sump drain with multiple perforations. It was directed toward the cul-de-sac. The lavage fluid consisted of the following amounts of anhydrous materials per

of fibrin which formed in spite of the initial dosage. This amount of heparin did not alter the patient's bleeding time.

Seligman *et al.*²⁰ in his work with dogs found that the most efficient rate of lavage was somewhere between 25 and 40 cc. per minute, re-

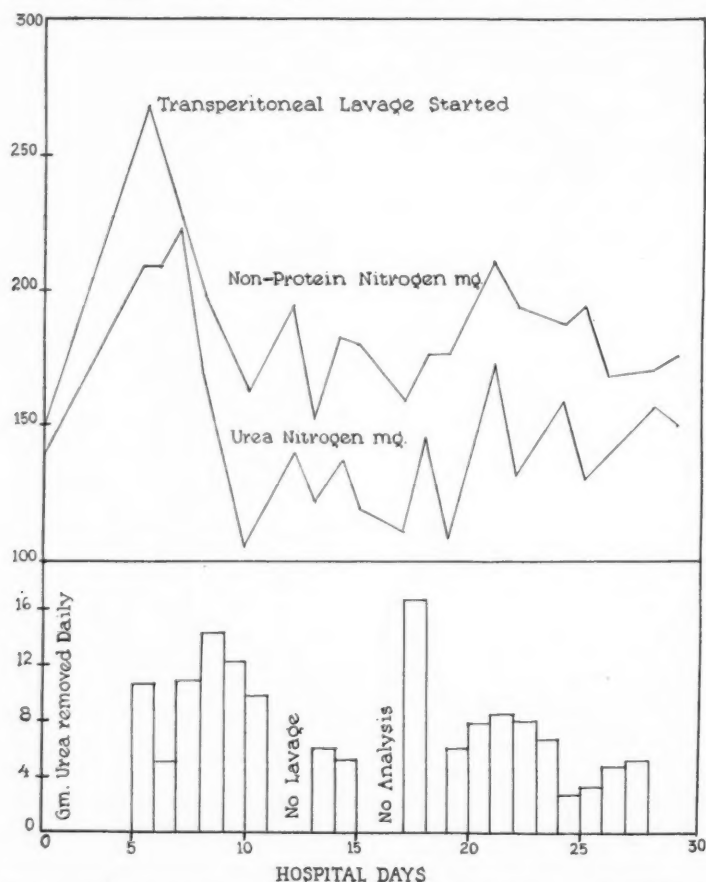


FIG. 2. The above curves illustrate the trend of the concentration of non-protein nitrogen products in the blood as well as the daily amounts of urea removed by lavage.

liter of fluid: sodium chloride, 8.0 Gm., potassium chloride 0.2 Gm., calcium chloride 0.1 Gm., magnesium chloride 0.1 Gm., sodium dihydrogen phosphate 0.05 Gm., sodium bicarbonate 1.0 Gm. and dextrose 1.5 Gm. In addition 10,000 units of sodium penicillin and 0.14 Gm. of sodium sulfadiazine were added per liter of lavage fluid to combat any contaminants which might be introduced into the fluid during their preparation. It is believed that these were most important in averting or at least delaying the onset of peritonitis. Sodium heparin in a concentration of 0.5 mg. per cent was added to minimize the formation of fibrin and thus prevent the tubes from becoming clogged. It was later found necessary to double this dose of heparin to prevent the small amount

quiring a total of 36 to 58 L. of fluid per day. Volumes below this were inefficient and volumes above were of no particular benefit. We planned to pass 40 L. per day through this patient. Putting this amount of fluid through the peritoneal cavity presented no problem as long as the suction pump continued to remove it. Much larger volumes could have been passed had it been necessary.

When the lavage was started the non-protein nitrogen reached a high of 266 mg. per cent, the urea 248 mg. per cent and creatinine 23 plus mg. per cent. Figures 2 and 3 illustrate the results obtained with the lavage. It will be seen that a rather rapid drop from the high nitrogenous values was quickly realized. The later more gradual drop was due in part to pump

failure and also short-circuiting of the lavage fluid. Upon investigation the influent tube was found lying anterior to the omentum. It is believed that if placed posterior to it more dialyzing surface would be available and thus more nitrogenous products would be removed.

the usual vitamins in large doses. The anemia was controlled as long as transfusions were available.

The patient showed marked improvement clinically the second day after lavage was instituted. He became rational, his appetite im-

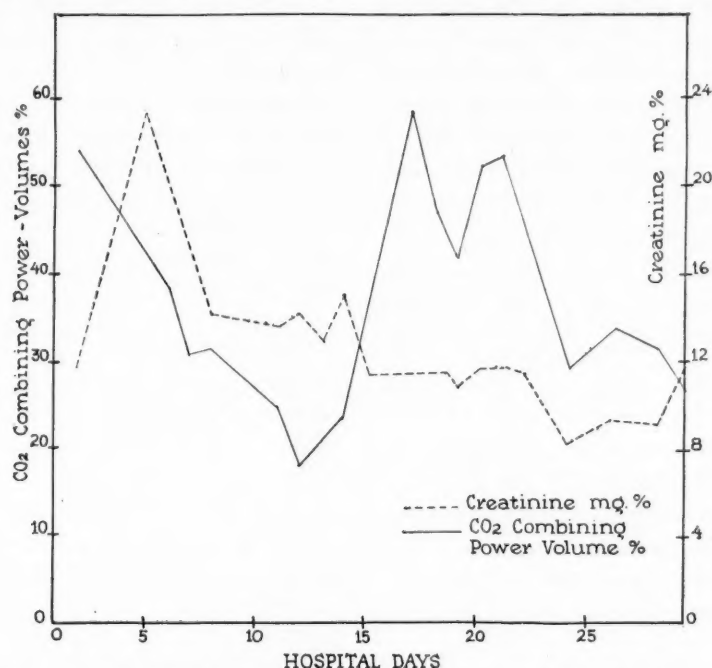


FIG. 3. Illustrating the blood creatinine levels and CO₂ combining power.

It was found that a considerable amount of difficulty was experienced in keeping the effluent tube in the cul-de-sac. Since it kept working itself to the surface, it was finally allowed to remain in that position at which time a definite track was formed about it by the omentum. It worked very well in this position. Had the tube been directed to the cul-de-sac from the flank position instead of from the midline, this earlier difficulty might have been avoided. On the fourteenth day of lavage the flow was interrupted for thirty-six hours. The non-protein nitrogen and urea nitrogen blood levels again showed a rapid rise. This was reduced when lavage was resumed. Acidosis was a problem early in the treatment contrary to expectations with the use of buffered lavage fluid. However, this was easily corrected with the use of sixth molar sodium lactate solution. The patient was only mildly edematous from time to time in spite of the rather large volumes of intravenous fluids used to correct the marked anemia, acidosis and to stimulate diuresis. During the entire period, penicillin was given intramuscularly as well as

proved and he tolerated food very well. He did not object to the treatment and from time to time would aid in the adjustment of the apparatus. On the eighth day of peritoneal lavage he developed an ileus. Wangenstein suction was started and continued for seven days. At the end of this time bowel sounds returned and the patient resumed taking food well and having normal bowel movements. On the eleventh day of lavage his blood pressure dropped from its usual high level and remained at 160 systolic and 110 diastolic. The blood creatinine showed the most constant drop throughout the period of treatment. This would be expected insofar as it is the last to rise in renal failure. The non-protein nitrogen and urea nitrogen did not show the rapid and steady decrease in the latter half of the treatment as it did in the beginning. This probably was due to the fact that there was a rapid unloading of nitrogenous products from the extracellular fluid stored there during the height of azotemia and also because of the high protein diet and parenteral administration of amino acids during

the later stages of treatment given to combat emaciation.

At no time was the urinary output sufficient to sustain life. The patient became anuric on the third hospital day and remained so until the third day of lavage. At this time he voided 420 cc. which was encouraging. The urine proved to be of better quality than we anticipated. The specific gravity was 1.016 and contained 0.5 Gm. of urea. It was free from sugar but did contain 300 mg. per cent of albumin, some red blood cells and granular and hyaline casts. The specific gravity and urea content did indicate some functioning renal tissue. The following sixteen days he averaged a urinary output of 150 cc. per day. After this time his output became progressively less and during the final three days of treatment was only 50 cc. per day. This obviously was insufficient to prevent azotemia.

Calculations for blood urea clearance by lavage of the peritoneum showed that our set-up was not as efficient as that reported by Seligman and his group.²⁰ The maximum clearance we could attain was 11.0 cc. of blood per minute. Our average clearance was in the vicinity of 8.5 cc. of blood per minute.

The effluent lavage fluid had the appearance, color and odor of urine. It always had a slight turbid appearance which was due to fibrin and other proteins. Only a trace of protein could be demonstrated at any time. The specific gravity was unaltered in passing through the peritoneal cavity. It was found to be sterile on all occasions with the exception of the eleventh day of lavage. This was the third day following the onset of the ileus. Culture of this effluent lavage fluid showed a medium growth of *Bacillus alkaligenes* and *Pseudomonas pyocyaneus*. Cultures on later days failed to confirm this. At the time the lavage was temporarily interrupted on the fourteenth day of treatment, 1.0 Gm. of streptomycin in 1 L. of lavage fluid was instilled into the peritoneal cavity without untoward effects. The blood sulfadiazine level never exceeded 2.4 mg. per cent. In the earlier days of treatment when the dextrose content of the lavage fluid was maintained at 1.5 Gm. per L. practically all of it was absorbed. Later, when a more hypertonic solution was used to combat edema and nutritional acidosis, the dextrose content was increased to 20.0 Gm. per L. At this concentration the peritoneum failed to absorb all of the sugar. Approximately 40 to

50 per cent passed through with the effluent fluid unabsorbed.

With the onset of the twenty-second day of lavage the patient became progressively more edematous. Pulmonary edema did not become evident until the twenty-sixth day of lavage. At this time the patient became more dyspneic and in spite of all measures suddenly expired.

The autopsy findings were in accordance with our earlier impressions. The anatomic diagnosis was that of a malignant nephrosclerosis. There was a fibrinous and fibrous peritonitis, pleuritis and pericarditis, marked hypertrophy and cloudy swelling of the myocardium and dilatation of the left ventricle. There was a bilateral hydrothorax. In addition there was metastatic calcification of the kidneys and the lining and myocardium of the heart, mural thrombi of the right auricle and right auricular appendage. There was a moderate atherosclerosis of the aorta and its main branches; verrucous endocarditis of the posterior leaflet of the aortic valve, hyperemia of the lungs; cortical adenoma of the right suprarenal gland, fibrous thickening of the aortic, mitral and tricuspid valves; glandular hyperplasia of the prostate.

The histological diagnosis confirmed these findings.

COMMENT

The autopsy findings make it apparent that the kidney damage in this patient was definitely irreversible. It is interesting to note and of definite value, too, that this patient was able to live an additional twenty six days without material aid from his own renal tissues. His existence during this time was not too trying or uncomfortable. Had the damage been of a reversible nature, twenty-six days would have been more than ample for the damage to be repaired. One of the difficult decisions to make in dealing with patients developing azotemia is when treatment of this nature should be instituted. The proper time has not been established. It is not possible to say when any given data regarding the uremic state signify the existence of irreversible damage. Therefore, since the procedure can be carried on for many days safely, as illustrated by this case, it probably should be

started soon after the azotemia is definitely established. Meanwhile, it is important not to add to the patient's problems by excessive fluid administration since the amount of water needed is small and as a diuretic in anuria it has proved futile.

The maintenance of proper electrolyte balance of the extracellular fluid will probably be the key to success in most cases treated by this method. A common error, as we experienced, is the ambitious administration of parenteral fluids. In retrospect we now appreciate that the only fluids required were those to correct the acidosis and blood transfusions to improve the severe anemia present. Much more accurate information as to the state of hydration of the patient can be obtained from studies of the volume of extracellular fluid by means of radioactive sodium or by the other means now available. These data would be of invaluable assistance in altering the composition of the lavage fluid. Gamble, in a personal communication to Fine, stated that in uremia the defense of the chemical structure of the extracellular fluid is of much more importance from the point of view of survival than reduction of azotemia.

In the past the chief danger considered in this method of correcting azotemia was that of bacterial peritonitis. Here again it has been demonstrated that with reasonable care in the preparation of the fluids and handling of the equipment this hazard can be readily eliminated. The use of penicillin and sulfadiazine salts aids in keeping the solutions sterile. Fine and his group use a bacterial filter interposed between the abdomen and the lavage storage bottle. This was not included in our equipment. Although it is an added protection, it was found to be unnecessary. In those instances in which the kidney has been sensitized to sulfa drugs in the past it will be necessary to avoid using materials of this kind in the lavage fluid. Streptomycin can be substituted in these cases. One culture of the effluent lavage fluid was found to contain *Bacillus alkaligenes* and *Pseudomonas pyocyaneus*. These organisms were

not found on repeated examinations following their initial discovery and may have been eliminated by the streptomycin which was instilled into the peritoneal cavity shortly after their presence was known. During the twenty-six days of operation of this equipment several members of the hospital staff were called upon at various times to prepare solutions, change bottles, etc. In spite of these opportunities for contamination no bacterial peritonitis developed. This may have all been due to the inhibitory action of the antibacterial agents in the lavage fluid as well as the constant dilution and exchange of fluid passing through the peritoneal cavity. Of the recent cases reported in the literature using this form of therapy, none reported the development of bacterial peritonitis as a cause of failure. Therefore, it can be concluded that with reasonable care and caution this hazard may be minimized.

No claim for originality for this method of combating azotemia is made by the present authors. The excellent work of Seligman, Fine and Frank has led to its present day understanding and application. It is apparent from our working with it, as well as other cases reported, that it is still a procedure lacking in perfection. A number of the difficulties will be removed with the development of a more efficient lavage fluid. In the meantime, however, this therapeutic procedure which utilizes the peritoneal membrane for removing non-protein nitrogenous materials from the blood stream and tissues in what would otherwise be a fatal azotemia should be resorted to with caution.

CONCLUSIONS

1. Continuous transperitoneal lavage was carried out for twenty-six days, resulting in a marked reduction of blood non-protein nitrogenous products. This period of time would have been ample for repair of a reversible kidney damage. The case reported had irreversible damage.

2. That a more efficient and better buffered lavage fluid is necessary for its

successful use is indicated by the development of acidosis and edema. Parenteral fluids in any form should be administered with caution.

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Acute Urinary Suppression*

Observations in Twenty-two Patients

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IN recent years there has been revival of interest in the treatment of acute urinary suppression by a variety of procedures. One approach has been directed toward the alleviation of nitrogen retention and correction of derangements in electrolyte patterns of the blood. The methods employed and the results obtained have been admirably summarized by Snapper.¹ Other efforts have been aimed at increasing urine formation by blocking neurogenic impulses to the kidney or by renal decapsulation, as set forth by Culpepper and Findley.² In the interest of providing a control series it seems timely to review the natural history of acute urinary suppression treated without these means.

The purpose of the present study is to determine the frequency with which severe urinary suppression is spontaneously reversible, to determine the length of time suppression may exist with spontaneous recovery, to record the maximum duration of suppression of urine compatible with life and to ascertain the cause of death in fatal instances.

Definition. Suppression of urine may be said to exist whenever the urinary output for a given period of time falls below the anticipated minimal requirement for urinary water. The magnitude of the solutes requiring urinary excretion and the concentrating ability of the kidney are the two factors that define minimal urine volume. Approximately 500 cc. of urine per day are required by a normal 70 Kg. man under conditions of fasting and thirsting so that

solute retention does not occur, as demonstrated by Gamble.³ This minimal urine volume of 500 cc. per day in the fasting state can be lowered to approximately 250 cc. by daily administration of 100 Gm. of glucose. Such carbohydrate has a protein-sparing action and prevents ketosis. By these two mechanisms the daily solute load and consequently the minimal urine volume are reduced approximately one-half. Further administration of protein and fat only serves to increase the formation of solutes ultimately designated for urinary excretion. For this reason 250 cc. approximates the absolute minimal amount of urine that can be formed under optimum conditions without solute retention. Any additional decrease in urine formation constitutes urinary suppression.

Under conditions of thirsting, with an intake of 100 Gm. of glucose, fluid in the form of urine and insensible water is lost at the expense of preformed body water. Gamble demonstrated that a water intake up to 750 cc. will spare an equivalent amount of preformed body water without increasing fluid loss.³ Any water intake in excess of 750 cc. is excreted in the urine. Thus, in terms of fluid intake for a 70 Kg. man receiving 100 Gm. of glucose daily, suppression of urine occurs whenever the daily urine output is less than 250 cc. plus any water consumed in excess of 750 cc. As many clinical disorders are associated with changes in protein breakdown, solute load and extrarenal water loss, determination of minimal urine volume becomes more

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complex and the definition of urinary suppression impossible without more specific information.

Selection of Patients. Each case was chosen from the records of the Columbia-Presbyterian Medical Center. Only adult patients

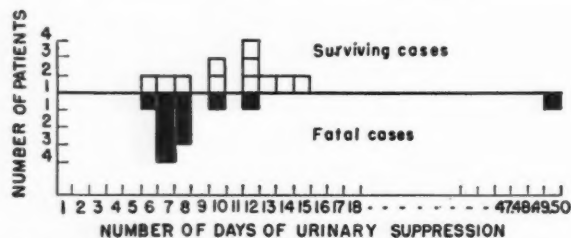


FIG. 1. The duration and outcome of urinary suppression in twenty-two patients.

who had a measured urinary output of less than 100 cc. a day for three or more consecutive days under direct hospital observation were included in this study. In each instance retention of urine within the bladder was excluded by catheterization. Twenty-two patients fulfilling these criteria were found. The various causes of urinary suppression that were encountered in this series are listed in Table I.

Duration. Analysis of the daily urinary output of each individual patient disclosed that diuresis occurred gradually in step-like fashion over a span of four to seven days. It was not until the end of this period that the kidney was able to excrete maximum volumes of urine in the neighborhood of 5,000 to 6,000 cc. It was arbitrarily decided to call the onset of diuresis, or end of a period of urinary suppression, the first day in which the urine volume exceeded 1,000 cc. after a period of three or more days with a urine output of less than 100 cc. daily.

Figure 1 illustrates that in these twenty-two patients the duration of urinary suppression varied between six and fifty days. Eleven patients with severe depression of urine formation lasting from six to fifteen days completely recovered. Eight of these patients exhibited suppression of urine formation for ten or more days. In one patient (G. M., Fig. 2) urinary suppression persisted over a period of more than fifty consecutive days. This patient lived for

forty-nine days with a urinary output of less than 200 cc. on any one day, and for thirty-one days there was absolutely no excretion of urine whatever. Postmortem examination disclosed complete ureteropelvic obstruction with hydronephrosis due

TABLE I
FREQUENCY OF VARIOUS CAUSES OF URINARY SUPPRESSION
IN TWENTY-TWO PATIENTS

Cause	No. of Patients
Transfusion with incompatible blood	6
Postpartum urinary suppression	3
Carbon tetrachloride poisoning	2
Diabetic acidosis with shock	2
Sulfonamide nephrosis	2
Hemolysis due to sulfanilamide	1
Mercury bichloride poisoning	1
Pentachloronaphthalene poisoning	1
Bacitracin toxicity	1
Acute glomerulonephritis	1
Shock, peritonitis and ileus	1
Bilateral ureteropelvic obstruction	1

to bilaterally aberrant renal arteries and veins. The capacity of each dilated renal pelvis was not more than 500 cc. With this single exception, urinary suppression did not last longer than twelve days in any of the eleven fatalities. In eight instances death occurred before the eighth day of urinary suppression.

Causes of Death. There were eleven deaths in twenty-two patients, a mortality rate of 50 per cent. An attempt to define the accurate cause of death was made in each fatality. Autopsies were performed on nine patients. In the two instances in which postmortem examination was refused clinical examination easily ascertained the cause of death—pulmonary edema and generalized peritonitis, respectively.

Table II illustrates that pulmonary infarction, generalized peritonitis and pulmonary edema secondary to excessive fluid administration account for five deaths (45 per cent). Of the remaining six patients two fatalities apparently resulted from multiple causes in which uremia probably played a part. One (A. G., Fig. 3) was a sixty-two year old male whose urinary suppression resulted from severe hemolytic anemia secondary to sulfanilamide sensi-

tivity. This patient died with a serum non-protein nitrogen level of 380 mg. per cent after eight days of urinary suppression. His hospital course was complicated by the appearance of auricular fibrillation with marked congestive cardiac failure and

hospital in coma resulting from a type xxii pneumococcus bronchopneumonia and arteriosclerotic heart disease, with pulmonary congestion, peripheral edema, auricular fibrillation, left bundle branch block and a venous pressure elevation of 230 mm. of

TABLE II
RELATIONSHIP BETWEEN THE CAUSE OF DEATH, MAXIMUM DEGREE OF NITROGEN RETENTION AND DURATION OF URINARY SUPPRESSION IN ELEVEN FATALITIES

Name	Age	Cause of Urinary Suppression	Cause of Death	N.P.N. B.U.N. (mg. %)	Days before Death	Duration of Suppression	Autopsy
G. M.	31	Ureteropelvic obstruction	Uremia	227	3	50 days	Ureteropelvic obstruction due to bilaterally aberrant renal arteries and veins
W. L.	55	Transfusion reaction	Pulmonary edema	150	0	12 days	Pulmonary edema, "hemoglobin nephrosis"
H. S.	51	Transfusion reaction	Generalized peritonitis following pancreatectomy	132	1	10 days	Generalized peritonitis, "hemoglobin nephrosis"
C. H.	79	Transfusion reaction	Sudden, unexplained	120	1	8 days	"Hemoglobin nephrosis," acute right pyelonephritis and acute cholecystitis
M. J.	63	Sulfadiazine nephrosis	Pulmonary emboli	96	2	8 days	Multiple pulmonary emboli and infarctions, sulfadiazine nephrosis
A. G.	62	Intravascular hemolysis due to sulfanilamide	Anemia, congestive failure and uremia	380	1	8 days	"Hemoglobin nephrosis," congestive cardiac failure
E. R.	53	Acute glomerulonephritis	Sudden, unexplained	145	1	7 days	Absent left kidney, acute glomerulonephritis, right
A. S.	24	Postpartum suppression	Sudden, unexplained	136	1	7 days	"Lower nephron nephrosis"
C. F.	86	Sulfathiazole nephrosis	Pneumonia, cardiac failure and uremia	190	1	7 days	Sulfathiazole crystals in tubules, ureter and bladder; bronchopneumonia, arteriosclerotic heart disease with congestive failure
R. B.	57	Shock, peritonitis, ileus	Generalized peritonitis after abdominal operation	104	2	6 days	None
M. T.	32	Postpartum suppression	Pulmonary edema	80	4	7 days	None

venous pressure elevation to 240 mm. of water following excessive fluid administration. The second instance was that of an eighty-six year old male who entered the
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water. After seven days of hospitalization, during which time he was unconscious, the patient developed urinary suppression due to sulfathiazole administration. He died

seven days later with a serum non-protein nitrogen level of 190 mg. per cent. In the face of major extrarenal complications it would be incorrect to ascribe either of these two deaths to uremia alone.

Three patients died suddenly over a

potassium intoxication as the cause of death in these three instances. Postoperatively, one of these patients, a seventy-nine year old male, had a complicating acute cholecystitis and pyelonephritis at autopsy. In the other two patients no anatomic cause

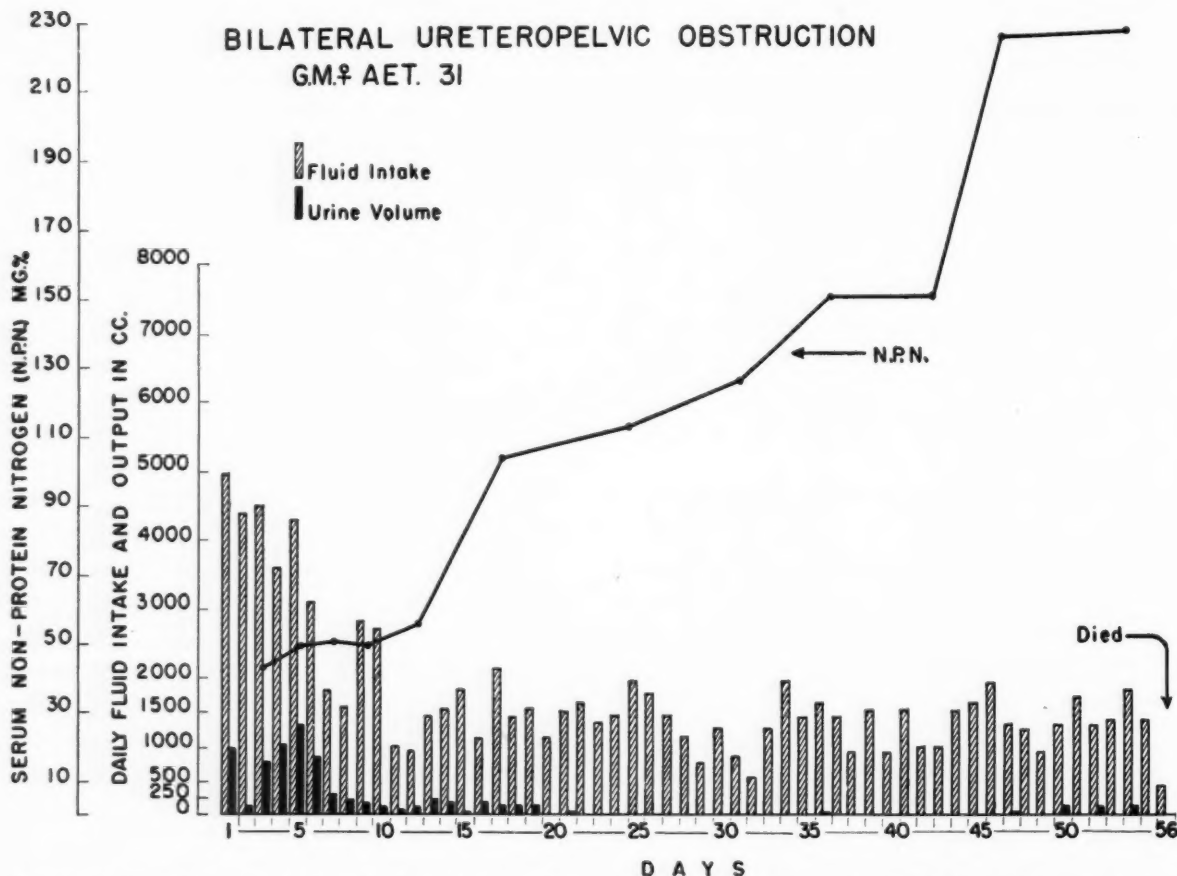


FIG. 2. This patient was admitted for investigation of extensive ankylosing rheumatoid arthritis and for regulation of diabetes mellitus in mild acidosis. She gradually developed progressive urinary suppression, azotemia and peripheral edema without other signs of circulatory failure or abnormalities of blood pressure. Ankylosis of both hips prevented cystoscopy. She was given no parenteral fluids and remained completely rational until two days before death. Autopsy examination identified congenitally aberrant renal arteries and veins bilaterally, producing complete ureteropelvic obstruction. The serum potassium was 5.7 mEq./L. prior to death.

period of several minutes to one hour with serum urea nitrogen levels of 120 and 145 mg. per cent and a non-protein nitrogen level of 136 mg. per cent, respectively. Immediately preceding death the clinical condition of each patient was thought to be satisfactory. The level of nitrogen retention in each instance was below the general average of nitrogen retention. Failure to take electrocardiographs and to obtain serum potassium levels prior to death precluded the possibility of establishing

for death was found at postmortem examination other than the renal lesion.

The last fatality, ending in uremia after fifty days of urinary suppression due to bilateral ureteropelvic obstruction, has been mentioned. (G. M., Fig. 2.) In all of the eleven surviving patients with so-called "lower nephron nephrosis" the early appearance of diuresis prevented urinary suppression of this duration from taking place. In each instance of urinary suppression in this series resulting from lower nephron

nephrosis diuresis occurred within sixteen days. In all instances death occurred before the twelfth day. (Table III.)

In summary, of eleven deaths five were due to pulmonary edema or to completely unrelated coexisting fatal diseases. Three

elderly patients died with uremia and severe cardiac failure, one complicated by pneumonia and the other by marked anemia. Only one death may be solely ascribed to uremia and this did not occur until after the fiftieth day of severe urinary suppression.

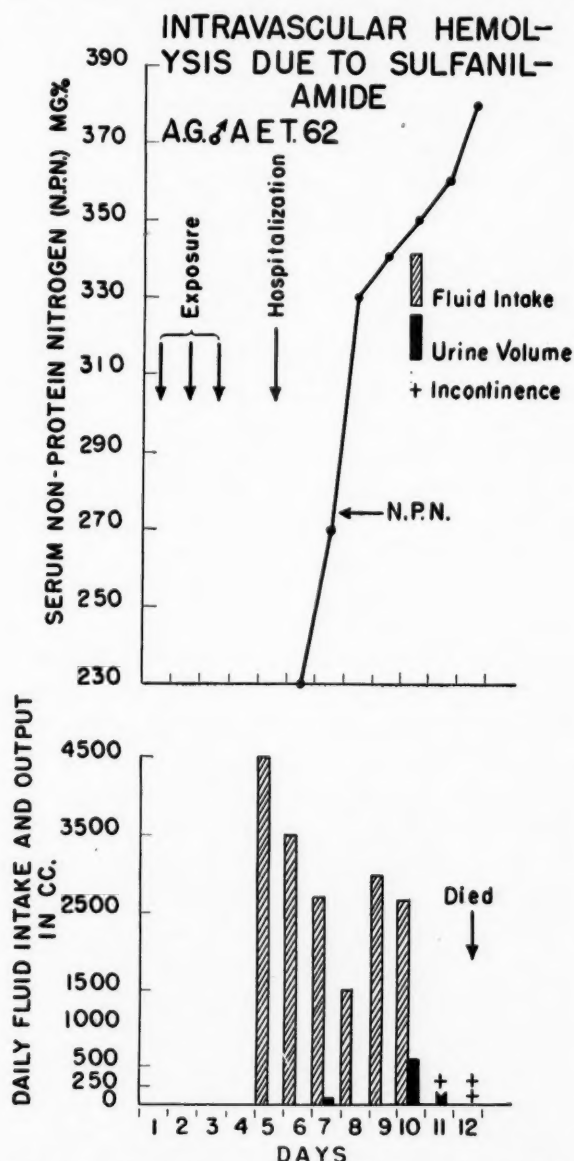


FIG. 3. This man was given oral sulfanilamide for a skin infection starting four days before admission. He developed a severe, acute hemolytic anemia ending fatally in urinary suppression. The excessively high level of serum N. P. N. probably resulted from massive blood destruction.

deaths occurred suddenly with degrees of nitrogen retention below the general average for surviving patients so that potassium intoxication may have played a role. Two

TABLE III
RELATIONSHIP BETWEEN MAXIMUM DEGREE OF NITROGEN RETENTION AND DURATION OF URINARY SUPPRESSION IN ELEVEN SURVIVING PATIENTS

Name	Age	Cause of Urinary Suppression	Maximum N.P.N. B.U.N. (mg. %)	Duration of Suppression
I. W.	18	Diabetic acidosis with shock	122	15 days
E. S.	32	Mercury bichloride poisoning	206	14 days
H. B.	29	Transfusion reaction	225	13 days
H. Q.	36	Carbon tetrachloride poisoning	192	12 days
L. H.	39	Transfusion reaction	113	12 days
G. G.	31	Postpartum suppression	139	12 days
M. T.	38	Pentachloronaphthalene poisoning	142	10 days
H. B.	33	Bacitracin toxicity	127	10 days
E. L.	34	Transfusion reaction	129	8 days
F. H.	63	Diabetic acidosis with shock	150	7 days
R. W.	37	Carbon tetrachloride poisoning	94	6 days

The conclusion seems warranted that urinary suppression relatively infrequently causes death unless the patient's health is otherwise jeopardized. This is supported by comparison of the ages of the surviving and fatal groups:

Average age of the entire group (22 patients) 44.7 years
Average age of the 11 survivors 35.4 years
Average age of the 11 fatalities 53.9 years

There were nine patients above the age of fifty. Of this group only one survived (89 per cent mortality). There were thirteen patients below the age of fifty. Of this group only three died (23 per cent mortality). The coexistence of underlying disease in the elderly with superimposition of urinary suppression accounted for most of the fatalities observed in that group.

CLINICAL FEATURES

Periorbital Edema. Of twenty-two patients, six had periorbital edema at a time when peripheral edema was slight or absent. Transfusion reaction and toxicity from

mercury, carbon tetrachloride and bacitracin accounted for the underlying disease.

Hypertension. Serial observations were made in all patients. Elevation of both the systolic and diastolic blood pressures above 140/90 occurred in thirteen instances. Hypertension was noted as early as the third day of urinary suppression and regularly subsided within twenty-six days. In three patients elevation of the blood pressure did not occur until after onset of diuresis.

Convulsions. Generalized convulsions in clonic and tonic phases were observed in five patients with and without associated hypertension. Three of these patients recovered.

Pericardial Friction Rub. A pericardial friction rub was noted in only one patient. This appeared on the twenty-third day of urinary suppression and persisted until death twenty-seven days later.

CHEMICAL STUDIES

Nitrogen Retention. Serial determinations of either the serum non-protein or urea nitrogen were made in every instance. No absolute correlation could be found between the duration of urinary suppression and the height of nitrogen retention. This might be expected as the rate of formation of non-protein nitrogen and its excretion varied tremendously from patient to patient. In the instance of A. G. (Fig. 3) excessive serum non-protein nitrogen formation, resulting from red blood cell destruction due to the hemolyzing effect of sulfanilamide, was reflected by a rapid rise in the serum non-protein nitrogen to a level of 380 mg. per cent on the eighth day of urinary suppression. On the other hand, considerable extra-renal excretion of nitrogen must have occurred in the instance of G. M. (Fig. 2), in whom the serum non-protein nitrogen reached a level of only 227 mg. per cent on the forty-seventh day of urinary suppression. In the latter instance the patient lost several hundred cc. of serous fluid daily from multiple subcutaneous blebs and needle puncture wounds. Ample amounts of this fluid were easily obtainable. Analysis on

one occasion disclosed that it contained 105 mg. per cent of non-protein nitrogen.

The general average of maximum serum urea nitrogen levels in the survivors was 155 mg. per cent. In the eleven fatalities only three attained levels higher than this whereas a serum urea nitrogen level of 225 mg. per cent, occurring in one surviving patient (H. B., Fig. 6), was greater than the highest value for nitrogen retention in all but one of the fatal cases. In most patients it was observed that the serum non-protein or urea nitrogen continued to mount during the early stages of diuresis.

Uric Acid. Retention of this substance paralleled that of the total non-protein nitrogen. Values as high as 20 mg. per cent were encountered.

Calcium and Phosphorus. Serial calcium and inorganic phosphorus determinations were made on nine patients. The degree of phosphorus accumulation and calcium depression tended to parallel that of the serum non-protein nitrogen. An increase in the serum inorganic phosphorus level to 12 mg. per cent and a reduction of serum calcium to 7 mg. per cent was encountered. Neither latent nor overt tetany was observed.

Sodium. Direct serum sodium determinations by flame photometry were made in only four instances. Values varied from 122 to 145 mEq./L. and seemed to be a reflection more of the sodium intake than of any other factor. Serum sodium levels could not be correlated with the onset of diuresis or the amount of clinical edema.

Potassium. Serial potassium determinations were performed in six patients, with mild elevation occurring in five. The highest value obtained was 7.4 mEq./L. Electrocardiographic tracings made in seven patients were available. Review of these records failed to disclose abnormalities that could be caused by only electrolyte disturbances. No data concerning potassium were available in any instance of sudden unexpected death.

Carbon Dioxide Content. The carbon dioxide content of the serum was determined serially in eleven patients. In the absence of

bicarbonate or lactate administration there was a consistent tendency for acidosis to occur, as reflected by a gradual decline in the serum carbon dioxide content. The magnitude of this fall was of the order of 20 volumes per cent, but in two patients levels

was, in part, the presumptive cause for the decline in the hematocrit and for the low plasma protein values observed in the sixteen patients measured. Because of the frequency of coexisting intravascular hemolysis in this series, the hematocrit was not

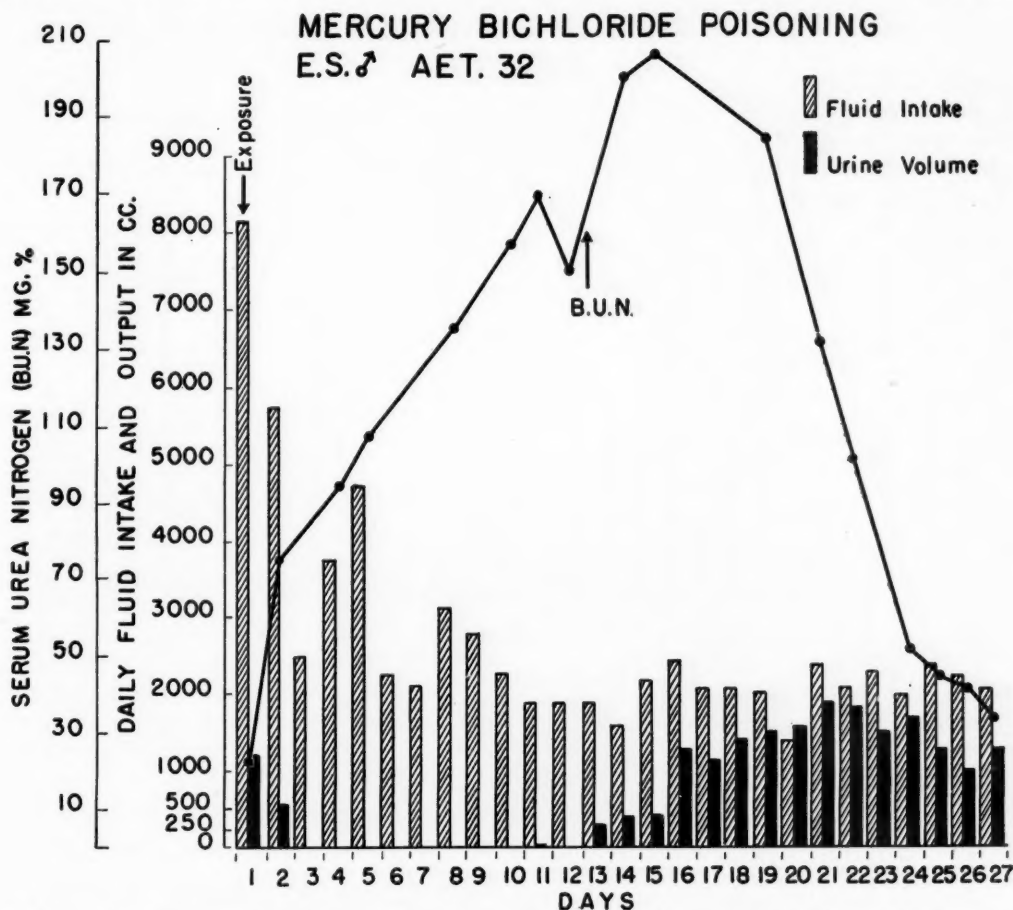


FIG. 4. This man consumed three tablets of mercury bichloride eight hours before admission and developed subsequent urinary suppression with complete recovery. He was given sodium thiosulfate daily. Mercury was identified in his urine.

of 17 and 18 volumes per cent were observed. As might be anticipated, administration of sodium chloride failed to correct this acidosis. Lactate and bicarbonate, on the other hand, produced a prompt elevation of the serum carbon dioxide content in each instance.

Chlorides. Serial determinations of the serum chlorides were made in ten patients. A general tendency to hypochloremia was observed, the lowest value being 77 mEq./L. Correction of the defect occurred promptly with administration of sodium chloride.

Hematocrit and Plasma Proteins. Hemodilution resulting from excessive fluid intake

always considered a reliable guide to further fluid therapy.

Fluid Balance. Of the twenty-two patients studied all except four developed peripheral edema. These four received an average fluid intake of 1,500 cc. daily in excess of measurable fluid loss. In three other patients administration of this same amount of fluid daily was associated with production of clinical edema. All of the remaining patients clearly received excessive fluids either parenterally or orally. All developed massive peripheral edema asso-

ciated with a 10 to 20 Kg. weight loss during the period of diuresis. (Fig. 4.)

Frank pulmonary edema due to excessive fluid administration was observed in three patients, resulting in two fatalities. A fluid intake of 2,000 to 3,000 cc. daily in excess

In the seven instances of urinary suppression due to intravascular hemolysis urinalysis was performed shortly after onset in six. In each of these six a guaiac test performed on the supernatant urine was strongly positive.

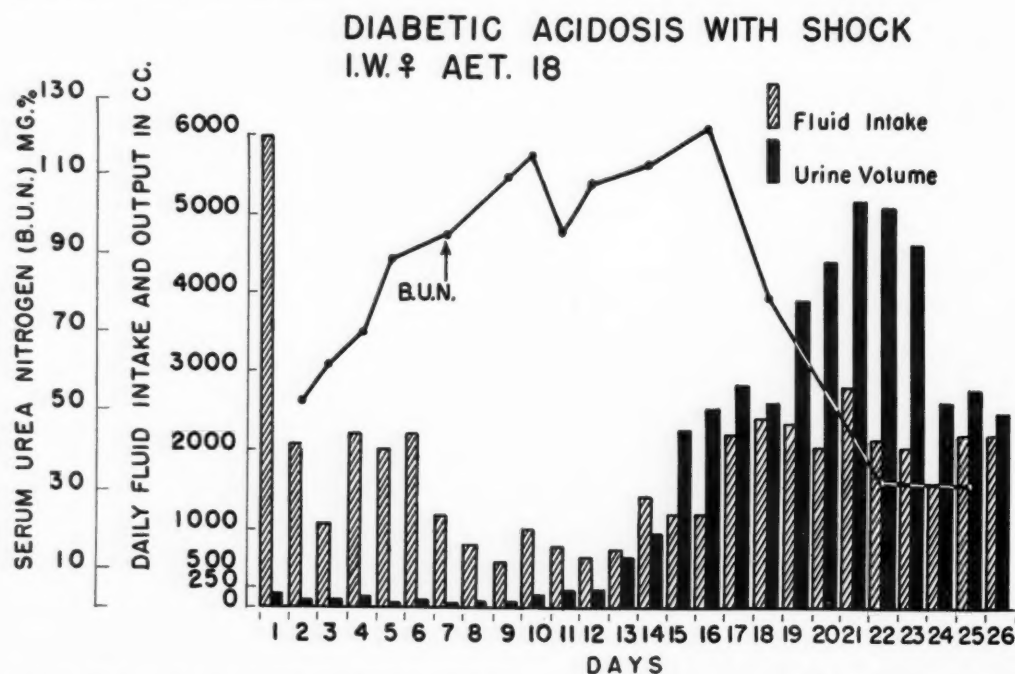


FIG. 5. This patient entered another hospital in marked diabetic acidosis and peripheral shock, responded well to routine treatment and was admitted two days later, at which time urinary suppression with peripheral edema was manifest. Her course was otherwise uncomplicated and recovery was complete.

of measurable fluid loss was found sufficient to produce this severe form of circulatory failure.

Venous pressures were measured in ten patients. Fluid in excess of 1,500 cc. was administered to nine of these patients, all of whom had unequivocal elevations of venous pressure, usually above 200 mm. of water.

Urine. Serial examinations of the urine were made in all twenty-two patients. Hyaline and granular casts were universally demonstrable but no other abnormalities were noted with this frequency. Red and white blood cells and albumin were present in almost all urines. Red blood cell casts were found only in association with acute glomerulonephritis. The specific gravity showed a tendency to fixation at 1.010 in almost all patients.

In both patients with diabetic acidosis it was observed that only minimal glycosuria and ketonuria were present despite demonstration of these substances in the serum in high concentrations. Similarly in all instances in which alkalization was attempted the scanty urine formed usually had an acid reaction to litmus paper despite serum carbon dioxide content levels of 70 to 80 volumes per cent. (Fig. 5.)

Treatment. The entire group was treated conservatively, with one exception. This patient (H. B., Fig. 6) had a transfusion with incompatible blood resulting in subsequent urinary suppression. On the ninth day a bilateral renal decapsulation was performed. Urinary output did not increase until the twelfth day, and 1,000 cc. of urine formation was not exceeded until the thirteenth day.

Postoperatively, a Miller-Abbott tube

was passed in two patients because of intestinal distention. In neither instance was the tube left in place for more than forty-eight hours, with total yields of 275 and 700 cc., respectively. Postoperatively, one patient who developed urinary suppression second-

Such treatment was not associated with diuresis in any instance.

In the remaining patients no attempts either to speed the onset of diuresis or create pathways for the extrarenal excretion of solutes was made. Treatment consisted of

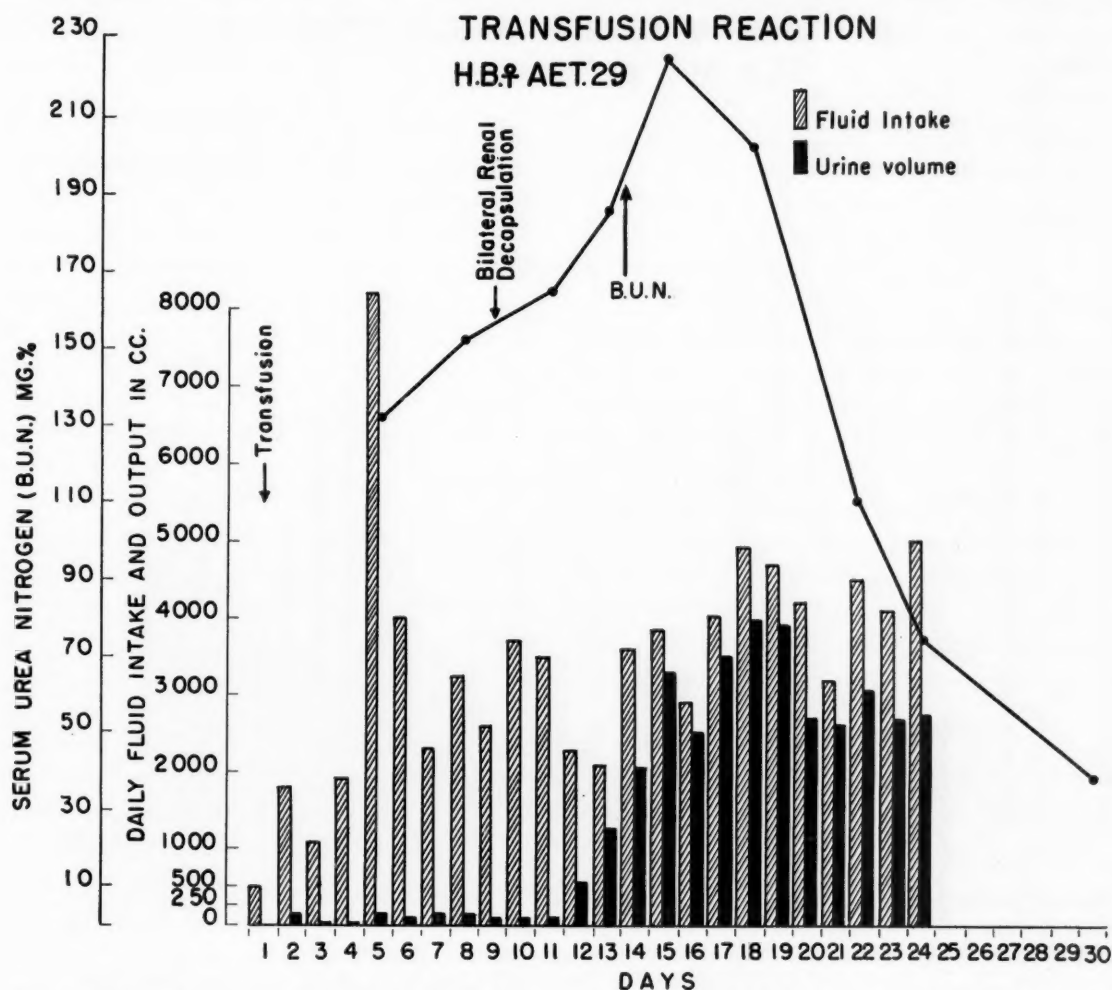


FIG. 6. This patient was admitted for uterine curettage and developed urinary suppression with complete recovery following a transfusion reaction. A bilateral renal decapsulation was not successful in initiating immediate diuresis. The diagnosis of "hemoglobin" nephrosis was substantiated by kidney biopsy.

ary to a transfusion reaction had a constant suction nasogastric tube in place throughout her course, with yields between 700 and 1,400 cc. daily. No definite effect on the serum non-protein or urea nitrogen level resulted from these inadequate attempts at gastrointestinal drainage.

The great majority of the twenty-two patients received intravenous injections of 50 per cent hypertonic glucose at some time during the period of urinary suppression.

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general supportive measures according to the clinical situation and was not carried out in conformity with any over-all plan. (Fig. 7.)

Follow-up. Of the surviving eleven patients satisfactory follow-up examinations up to sixteen years were obtained in all but one instance. Normal values for blood pressure, urinalysis, serum urea nitrogen, ability to concentrate urine and phenolsulfonphthalein excretion were observed at the

end of two to three months and usually sooner.

COMMENTS

These observations have been presented in order to ascertain the natural history of

has outlined. Should retention of solutes occur in excess of the average values observed here, the cause must lie not with increased severity of renal disease but with either excessive solute consumption or with excessive breakdown of body tissue.

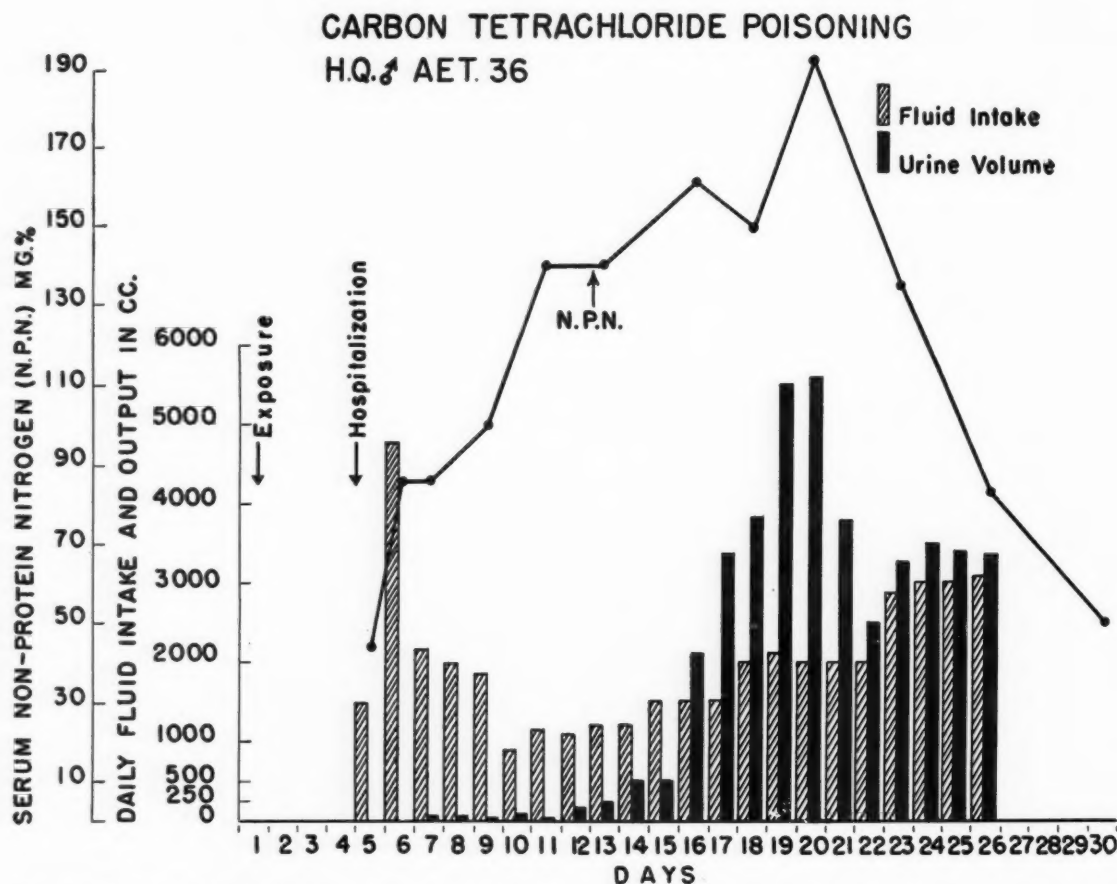


FIG. 7. This man inhaled the fumes of carbon tetrachloride in a closed room and developed subsequent urinary suppression three days before hospitalization. Frank pulmonary edema appeared during the early stages of diuresis but recovery was complete.

conservatively treated acute urinary suppression and to provide a control series for other methods of management currently advocated. The twenty-two patients described herein were selected as representing the maximum degree of suppression of urine formation and consequent loss of renal excretory function usually encountered clinically. Both from the standpoint of duration and magnitude of urinary suppression and from the degree of elevation of the serum non-protein or urea nitrogen, disease in these patients was of comparable severity to those treated by the methods Snapper¹

In this series approximately one-half of the deaths resulted directly from factors other than solute retention and could not have been prevented by any therapy directed at the alleviation of azotemia. In most of the remaining fatalities the retention of solutes was accompanied by severe co-existing physiologic disturbances in other systems of the body. Despite this fact the observed mortality rate of 50 per cent is considerably lower than the mortality rate for any published series thus far treated by the "artificial kidney," peritoneal dialysis, intestinal irrigation or exsanguinotrans-

fusion, as reviewed by Snapper.¹ It is clear, furthermore, that in one patient simple supportive measures were sufficient to sustain life for fifty days after the onset of severe urinary suppression although it should be added that seepage of edema fluid tended to ameliorate nitrogen retention. Several instances of similar long survivals have been reported in the literature and summarized by Strauss.⁴

In conclusion, analysis of the data presented herein indicates that urinary suppression is usually a self-limited disease when due to such causes as shock, intravascular hemolysis, postpartum eclampsia or poisoning by a variety of agents, including mercury bichloride. While diuresis occurs within two and one-half weeks in these conditions, life can be sustained without significant urine formation for a period of fifty days.

SUMMARY

1. Acute urinary suppression has been defined and observations recorded in a series of twenty-two patients exhibiting a measured urinary output of less than 100 cc. a day for three or more consecutive hospital days.

2. Twenty-one patients were treated conservatively without attempts either to speed the onset of diuresis or to create pathways for the extrarenal excretion of solutes. One patient underwent a bilateral renal decapsulation and diuresis occurred three days later.

3. Urinary suppression up to fifteen days' duration was associated with complete recovery in eleven patients.

4. Death ensued between the sixth and twelfth day of urinary suppression in ten instances.

5. The main causes of death as observed in this series were pulmonary edema resulting from excessive fluid administration and coexisting unrelated severe disease, such as generalized peritonitis and pulmonary embolism.

6. Urinary suppression of fifty days' duration was found compatible with life in one patient in whom bilateral ureteropelvic obstruction was demonstrable at autopsy. Seepage of edema fluid in this patient may have postponed exitus.

7. In the absence of severe coexisting disease, excessive fluid administration and unusually large amounts of tissue protein breakdown, spontaneous diuresis with complete recovery generally occurred. Consideration should be given to the usual favorable outcome of uncomplicated, conservatively treated, acute urinary suppression in evaluating the indications for and results obtained by the artificial kidney, peritoneal dialysis, intestinal irrigation, exsanguinotransfusion and similar procedures.

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Clinical and Metabolic Study of 11-Dehydro-17-hydroxy-corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus*

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SINCE the isolation of 11-dehydro-17-hydroxy-corticosterone (Compound E of Kendall),¹ its administration has been associated with effects on protein and carbohydrate metabolism in both normal and adrenalectomized animals.²⁻⁸ These studies have in general revealed weight loss, suppression of growth, glycosuria, hyperglycemia with altered glucose tolerance, increased nitrogen excretion, increased urinary excretion of sodium and chloride, and sometimes ketonuria. Thorn and his associates have reported improvement in carbohydrate metabolism in patients with Addison's disease.^{9,10}

The present study was undertaken in order to determine the clinical and metabolic effects of synthetic 11-dehydro-17-hydroxy-corticosterone acetate administered to human subjects. Because of the possibility that this steroid might depress the arterial tension¹¹ in addition to its apparent effects on carbohydrate metabolism, observations were made on two patients with uncomplicated hypertensive vascular disease, one with Addison's disease and one with diabetes mellitus and hypertensive vascular disease.

CASE REPORTS

CASE I. C. Z., a forty-three year old woman, was admitted to the metabolism ward of the Presbytrian Hosptial because of dizziness, headaches and hypertension known for six years. There was neither past nor present evidence of cardiac pain, congestive failure, or renal, cerebral or obvious endocrine disease. Physical examination was not remarkable except for a blood pressure of 220/130, marked arteriolar narrowing and arteriovenous compression on fundoscopic examination, and cardiac enlargement with a faint apical systolic murmur.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal arterial pressures were not reduced. X-ray of the heart disclosed moderate hypertrophy, chiefly of the left ventricle, but the electrocardiogram showed no significant abnormalities. Repeated urinalyses were negative; the urine concentrated to a specific gravity of 1.024; the phenolsulfonphthalein excretion was 70 per cent in two hours; and the intravenous pyelogram was normal. A benzodioxane test¹² did not suggest the presence of a pheochromocytoma.

The patient was kept in bed until after blood studies and blood pressure measurements were

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made, and ambulatory activity was standardized at a constant level the rest of the day. She was weighed daily before breakfast on the same scales. Distilled water was supplied for drinking. "Resting" blood pressures were measured each morning in the same arm by the same observer,

Sodium chloride was administered in constant amounts using weighed salt shakers.

After the preliminary period the patient was started on two baseline periods (I and II) of four days each. During a third and fourth four-day period (III and IV) she received 20 mg. of 11-

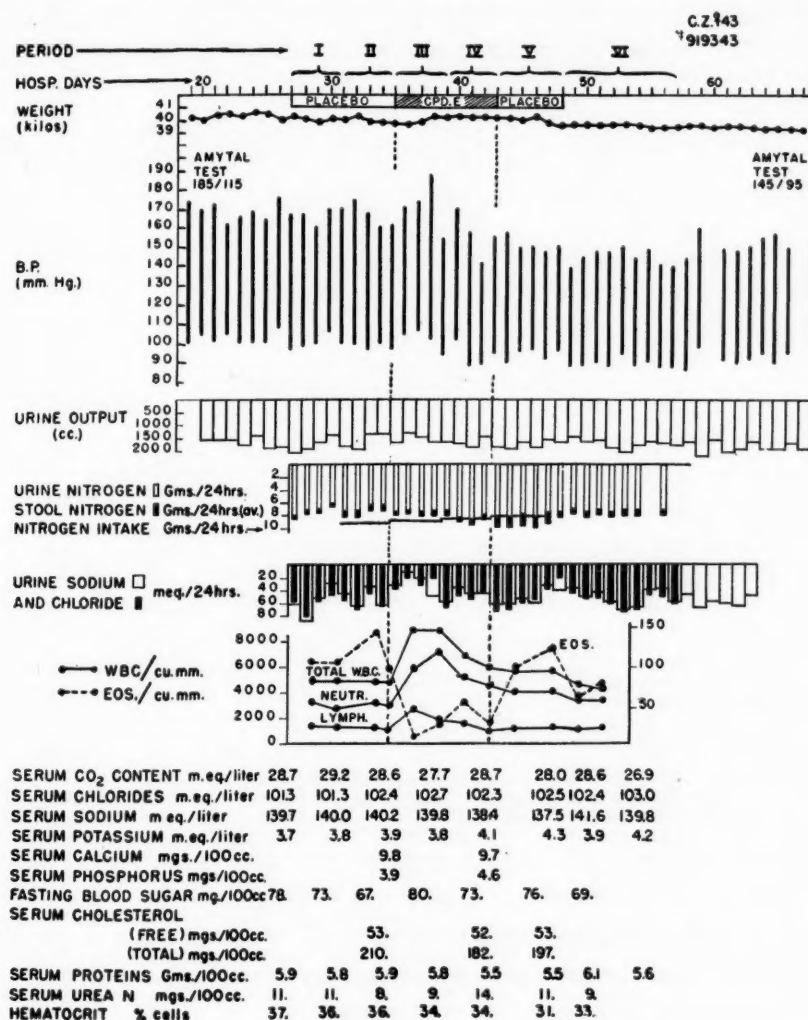


FIG. 1

with the subject quiet and relaxed in bed, the head of which was raised to a 30 degree angle. At least seven readings were taken at half-minute intervals and the lowest systolic and lowest diastolic values recorded. In order to secure an adequate baseline preliminary observations were carried out for twenty-seven days.

Throughout the study the patient was given a constant diet and fluid intake. Identical salt-poor daily menus (1,740 calories, including 50 Gm. of protein and 273 Gm. of carbohydrate) were prepared, the entire daily diet being subjected at intervals to direct chemical analysis.

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dehydro-17-hydroxy-corticosterone acetate intramuscularly at six-hour intervals. Final periods (v and vi) of five and ten days, respectively, served as post-treatment controls. Placebo intramuscular injections (1 cc. of 5 per cent glucose) were given during periods I, II and V.

Intravenous glucose tolerance tests were performed by administering 0.5 Gm. of glucose per Kg. of body weight in 200 cc. of distilled water over a thirty-minute period.⁹ On the day of these tests the diet was reduced by amounts of glucose and drinking water equivalent to those employed in the procedure and breakfast was

held until the completion of the test. Sodium and potassium determinations were made with an internal standard flame photometer having an accuracy of ± 1 per cent. The nitrogen in the diet, urine and stool specimens was determined

method of Daughaday and co-workers.¹⁴ White blood cells were counted in duplicate using standard technic, and eosinophiles* counted according to the method of Thorn and his associates.¹⁵

TABLE I(a)

Period	Hos- pital Day	Intake					Urine							Stool			
		Fluid	Na	Cl	K	N	Vol- ume	Na	Cl	K	N	17-keto- steroids	"Cor- ticoids"	Na	Cl	K	N
		Cc.	mEq./24 hr.		Gm./ 24 hr.		Cc.	mEq.		Gm.		Mg./24 hr. (av.)	Mg.	mEq./24 hr. (av.)		Gm./ 24 hr. (av.)	
I	27	2,250	2,130	60.5	59.5	67.3	8.14		2.88				
	28	2,250	1,940	85.7	80.3	59.4	7.38		2.30				
	29	2,250	1,720	52.3	56.3	51.9	7.07	7.03	2.13	2.7	0.9	7.2	0.75
	30	2,250	1,380	27.2	46.8	56.3	6.16		1.62				
II	31	2,250					1,810	43.4	55.3	73.8	7.76		1.98				
	32	2,250					1,980	62.8	69.2	63.7	7.34		2.61				
	33	2,250	58.9	62.5	66.7	9.34	1,320	33.4	43.9	57.7	6.55	10.66	1.79	4.3	1.6	10.0	1.07
	34	2,250					1,310	62.4	63.9	57.4	6.46		1.94				
III Compound E	35	2,250					1,660	33.1	37.0	72.4	7.52		2.10				
	36	2,250					1,290	11.0	19.7	43.5	7.36	6.37	1.49				
	37	2,250	59.4	60.9	63.2	8.92	1,440	19.9	32.9	44.8	7.70		1.61	1.4	0.7	6.1	0.65
	38	2,250					1,630	46.1	21.9	53.1	7.51	5.56	2.33				
IV Compound E	39	2,250					1,640	57.8	66.8	50.9	7.48		4.78				
	40	2,250					1,690	34.0	47.1	57.8	8.35	5.40	2.56				
	41	2,250	58.9	60.3	62.2	8.68	1,800	45.9	54.9	54.5	8.76		2.94	2.8	1.0	8.5	0.79
	42	2,250					1,460	46.0	46.6	40.6	8.03	7.55	1.39				
V	43	2,250					1,790	62.3	72.6	48.8	8.22		0.95				
	44	2,250					1,840	60.3	67.2	58.2	8.24	4.36	1.81				
	45	2,250	57.8	61.8	63.4	8.30	1,710	54.4	58.0	70.1	8.06		1.91	2.5	1.3	6.8	1.79
	46	2,250					1,800	58.3	56.0	73.8	8.10	4.57	1.16				
	47	2,250					1,560	34.0	37.9	57.0	7.63						
VI												6.14					
	48	2,250	1,620	40.5	40.7	68.0	7.74		1.67				
	49	2,250	1,490	36.1	45.3	59.0	7.02		1.28				
	50	2,250	1,690	48.0	53.4	60.0	7.57	6.54	0.89	3.0	1.4	7.6	0.70
	51	2,250	1,650	41.3	52.5	65.3	7.29						
	52	2,250	1,800	55.4	57.6	65.9	7.54		2.08				
	53	2,250	2,010	74.8	76.2	63.7	7.44	6.95	2.09				
	54	2,250	1,760	67.8	70.7	62.0	7.42						
	55	2,250	1,620	38.1	47.6	57.4	..		1.56				
	56	2,250	1,650	36.8	49.5	57.6	7.24						
	57	2,250	1,700	56.4	57.6	55.6	..		1.23				

by micro-Kjeldahl procedures. The stools for each experimental period were collected as a single specimen; 17-ketosteroids were estimated by a modification of the method of Callow, Callow and Emmens¹³ and "corticoids" by the

Results. The results are shown in Figure 1 and Table I. No subjective change was

* We are indebted to Mr. Paul Marks and Mrs. Dorothy Marks for these determinations.

noted. Compound E in the dosage employed (80 mg. daily) appeared to have a small but definite effect on water and salt metabolism. The weight increased; there was a suggestive decrease in urine volume

Nitrogen balance studies indicated an increased excretion appearing only after five days of treatment and persisting for about the same period after the administration of Compound E had been discontinued.

TABLE I(b)

Period	Hospital Day	Weight	“Rest- ing” B.P.	Sed. Rate	Hemato- crit	W.B.C.	Neutro- phils	Lympho- cytes	Eosino- philes	Blood Sugar and Glucose Tolerance					
										Fast- ing	½ Hr.	1	2	3	4
		Kg.	Mm. Hg	Mm./ hr.	% Cells	Cells/cu.mm.									
I	27	40.29	166/96	..	37	78					
	28	40.00	166/98	4,700	3,102	1,316	112						
	29	39.95	160/100												
	30	40.05	170/106	6	..	4,300	2,666	1,311	111	73	154	103	77	80	85
II	31	40.05	170/100	..	36										
	32	40.25	174/100												
	33	39.86	166/96	4,700	3,219	1,199	147						
	34	39.95	160/100	4,020	2,934	1,060	77	67	121	93	71	61	80
III Com- pound E	35	39.80	162/96	..	36										
	36	39.65	170/104	8,880	5,683	2,664	12						
	37	39.95	174/106												
	38	40.27	188/102	8,900	7,120	1,691	27	80	182	121	74	79	93
IV Com- pound E	39	40.20	154/94	..	34										
	40	40.25	170/102	6,900	5,106	1,518	59						
	41	40.24	156/88												
	42	40.26	140/88	5,820	4,598	931	25	73	154	97	58	75	68
V	43	40.25	154/94	7	34										
	44	40.13	156/92	5,480	4,000	1,205	90						
	45	40.00	148/96												
	46	40.30	150/96												
	47	39.90	146/92	5,500	4,015	1,330	125	76	154	85	60	64	74
VI	48	39.64	152/96	5	31										
	49	39.66	140/88	4,600	3,312	1,012	61						
	50	39.74	144/88												
	51	39.67	146/90	..	33	4,550	3,253	1,229	81	69	167	83			
	52	39.78	146/88												
	53	39.82	150/94												
	54	39.62	144/88												
	55	39.39	148/90												
	56	39.56	140/88												

and a definite decrease in urinary sodium and chloride; and evidence of hemodilution was obtained by changes in hematocrit and protein values.

Although a slight decrease in serum sodium and a suggestive increase in serum potassium concentrations were noted, serum electrolyte and calcium values were not

materially affected. There was an increase in the concentration of serum inorganic phosphorus. A slight decrease in total cholesterol was observed which was not at the expense of the free fraction. Urinary 17-ketosteroid and "corticoid" excretion did

teleroentgenograms and serial electrocardiograms were not modified.

A transitory increase in total white cell count, due primarily to a rise in polymorphonuclear leukocytes, immediately followed the use of Compound E, together with a sharp but more sustained drop in eosinophiles.

The "resting" blood pressure, after an initial rise, began to fall after the first period of steroid administration and remained at lower values throughout the post-treatment observation.

CASE II. P. K., a fifty year old laborer, was admitted because of heart consciousness, fatigue on exertion and hypertension of six months' known duration. Physical examination was normal save for a blood pressure of 235/140, moderate arteriolar thickening and arteriovenous compression on fundoscopic examination and cardiac enlargement without murmurs. There was neither past nor present evidence of cardiac pain, congestive failure, or renal, cerebral or obvious endocrine disease.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal artery pressures were not reduced. X-ray of the heart disclosed moderate cardiac hypertrophy; the electrocardiogram showed left axis deviation, a diphasic T wave in the first lead and inversion of the T wave in lead CF₄. Repeated urinalyses were negative; the urine concentrated to a specific gravity of 1.024; the phenolsulfonphthalein excretion was 50 per cent in two hours; and an x-ray of the renal area revealed the kidney shadows to be normal in size, shape and position with no evidence of calculi. A benzodioxane test was negative.

The conditions of the experiment were identical to those previously described except that Compound E (20 mg. intramuscularly at six-hour intervals) was administered for five days, beginning on the twenty-first hospital day, and less extensive studies were undertaken. The diet employed in this patient contained 2,175 calories per day which included 85 Gm. of protein and 267 Gm. of carbohydrate.

Results. The results are shown in Figure 2 and Table II. No subjective change was

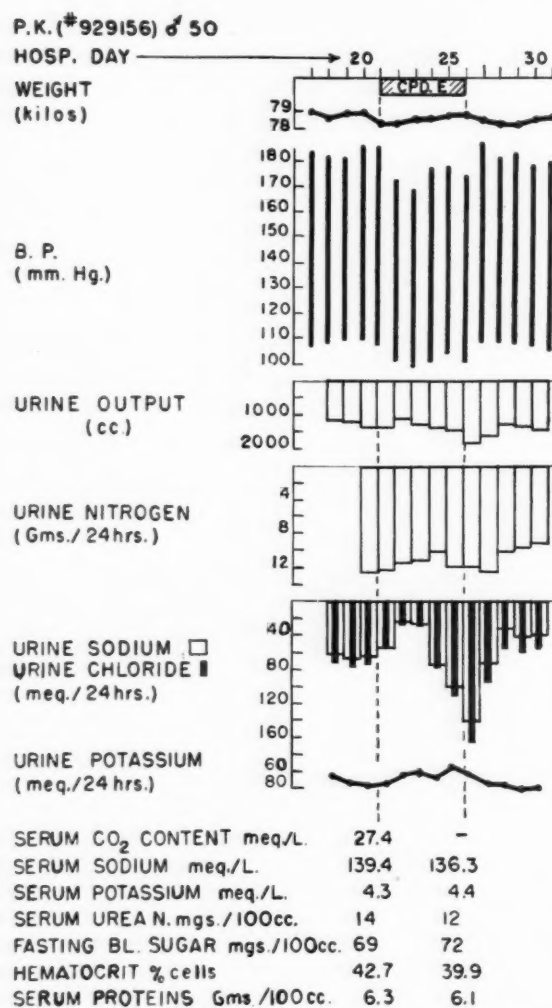


FIG. 2

not change to a great extent. On the fourth day of treatment the fasting and peak levels of blood sugar were higher than in other glucose tolerance tests but the results were of doubtful significance. The urine was analyzed daily for reducing substances, acetone and diacetic acid. All samples were negative with the exception of that obtained on the fourth day of treatment in which a trace of acetone was disclosed. The sedimentation rate remained unaltered and

noted. Compound E (80 mg. daily) appeared to have a small effect on water and a definite effect on salt metabolism. The weight increased slightly. There was a transitory small decrease in urine volume and a more marked retention of sodium

of steroid administration (at the same time as salt and water retention was observed) but returned promptly to baseline levels.

CASE III. J. R., a thirty-four year old, white clerk, had been in good health until seven years before the present study. At that time he de-

TABLE II

Period	Hos- pital Day	Weight Kg.	"Resting" B.P. Mm. Hg	Intake			Urine				
				Fluid	Na	N	Volume	Na	Cl	K	N
				Cc.	mEq.	Gm.	Cc.	mEq.			Gm.
I	17	78.85	184/106	1790	83.8	13.5					
	18	78.40	182/108	1790	83.8	13.5	1,210	62.6	71.5	65.3	
	19	78.89	182/110	1790	83.8	13.5	1,270	66.8	78.2	73.2	
	20	78.85	184/110	1790	83.8	13.5	1,370	64.4	74.9	78.4	12.7
II Compound E	21	78.25	184/106	1790	83.8	13.5	1,360	55.6	56.3	76.7	12.4
	22	78.20	172/102	1790	83.8	13.5	1,170	24.2	27.3	65.3	11.7
	23	78.50	170/100	1790	83.8	13.5	1,280	26.9	27.4	61.7	11.3
	24	78.60	178/102	1790	83.8	13.5	1,350	75.4	78.5	67.5	10.1
	25	78.85	178/104	1790	83.8	13.5	1,440	102.7	111.4	56.9	12.0
III	26	78.80	184/102	1790	83.8	13.5	1,850	143.8	166.0	63.9	12.0
	27	78.50	188/110	1790	83.8	13.5	1,600	74.2	92.6	76.4	12.6
	28	78.20	182/110	1790	83.8	13.5	1,240	34.5	57.9	77.4	10.1
	29	78.20	182/108	1790	83.8	13.5	1,300	45.7	59.1	82.2	9.7
	30	78.45	178/108	1790	83.8	13.5	1,450	43.8	57.7	79.4	
	31	78.60	180/106	1790	83.8	13.5	1,400	38.6	58.8	66.8	

and chloride during the first few days of drug administration. This was followed by a pronounced sodium and chloride (and to a lesser extent water) diuresis which began before the steroid was discontinued. Serum protein, hematocrit and urea nitrogen values suggested slight hemodilution.

Although nitrogen studies were limited to estimations of urinary excretion, the dietary intake being constant, no significant changes took place. There was a decrease in the serum sodium concentration. Fasting blood sugar values were not materially affected in this study. No glycosuria was produced but again a trace of acetone appeared in the urine on the fourth day of steroid treatment.

The "resting" blood pressure, which had fluctuated only from 180 to 190 systolic and 106 to 110 diastolic for several weeks before Compound E, fell slightly during the period

veloped weakness, fatigue, hypotension, nausea, skin and buccal mucous membrane pigmentation, and subsequently experienced several episodes suggestive of hypoglycemic reactions. The diagnosis of Addison's disease was clinically apparent and was substantiated by the finding of repeated serum sodium values which were markedly below normal limits. He was maintained in normal electrolyte and water balance by the subcutaneous injection of 2 mg. of desoxycorticosterone acetate* daily as well as by the addition to his regular diet of varying amounts of sodium chloride.

On this admission, except for the characteristic pigmentation and hypotension there were no abnormal physical findings. X-ray of the lungs and adrenal areas showed no signs of tuberculosis or abnormal calcification; the erythrocyte sedimentation rate was within nor-

* Furnished through the courtesy of Dr. K. W. Thompson of Roche-Organon, Inc., Nutley, N. J.

mal limits; and repeated urinalyses showed no abnormalities.

Throughout the study the patient was maintained on 2 mg. of desoxycorticosterone acetate subcutaneously each day and 8 Gm. of sodium chloride added to his identical salt-poor daily

muscularly at six-hour intervals) was limited to five days (period v).

Glucose tolerance tests were conducted as previously outlined, with the diet being reduced by amounts of glucose and drinking water equivalent to those employed in the procedure.

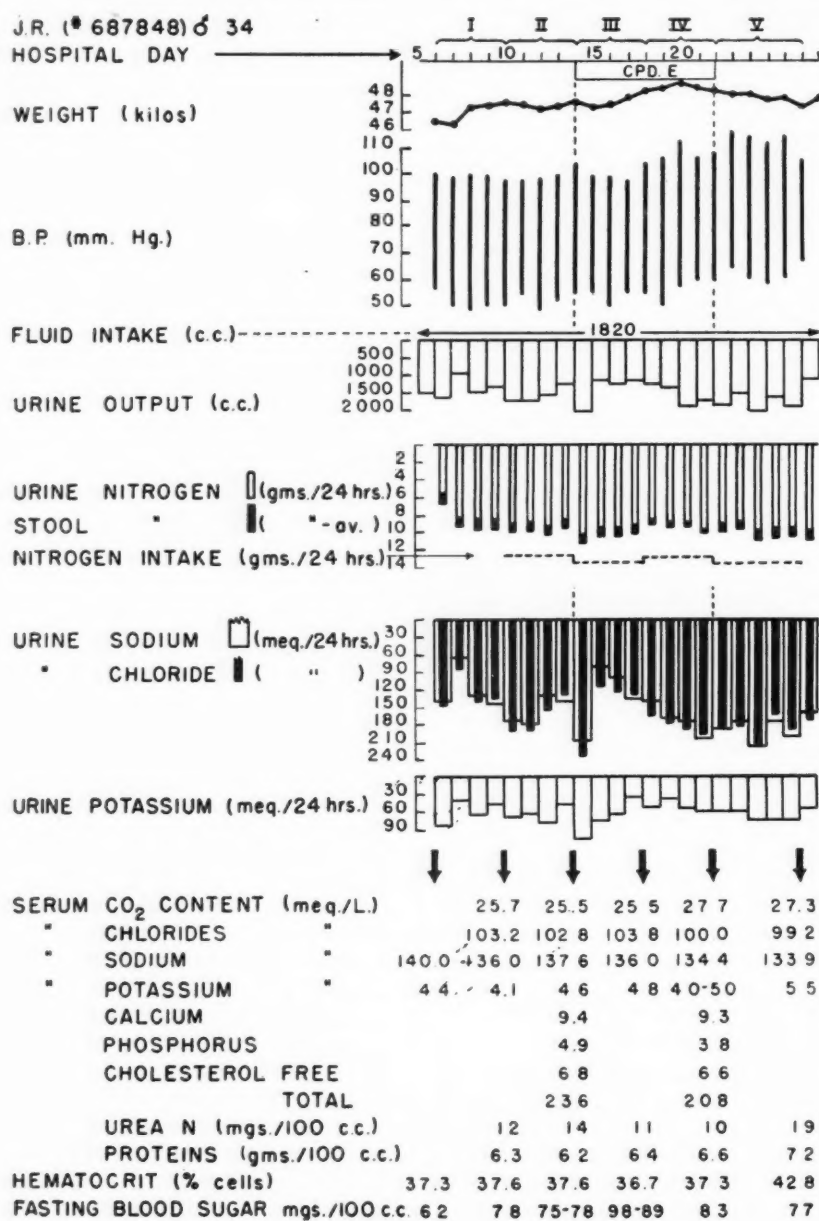


FIG. 3

menus. The daily diet contained 2,220 calories which included 75 Gm. of protein and 228 Gm. of carbohydrate. The conditions of the experiment were exactly the same as those described in the first patient except that period I began on the sixth hospital day and the length of observation after Compound E (20 mg. intra-

By finishing the previous day's diet at an earlier hour, all glucose tolerance tests began after a seventeen-hour period of fasting.

Results. The results are shown in Figure 3 and Table III. No subjective change was noted except for the development of moder-

ate insomnia. Compound E (80 mg. daily) appeared to have a definite effect on water and salt metabolism. There was a transitory increase in the excretion of water, sodium, chloride and potassium during the first twenty-four hours of steroid administration.

tained throughout the experiment with no apparent modification.

The serum sodium concentration began to fall toward the end of the period during which the patient received Compound E and continued to fall to subnormal levels

TABLE III(a)

Period	Hospital Day	Intake					Urine							Stools			
		Fluid	Na	Cl	K	N	Volume	Na	Cl	K	N	17-keto-steroids	"Corticoids"	Na	K	N	Fat
		Cc.	mEq./24 hr.			Gm./24 hr.	Cc.	mEq.			Gm.	Mg./24 hr. (av.)		mEq./24 hr. (av.)		Gm./24 hr. (av.)	
I	6	1,820	1,660	139.1	158.8	82.8	5.56						
	7	1,820	880	63.7	84.4	41.5	8.40						
	8	1,820	1,490	129.6	140.8	64.7	8.97			2.6	6.9	1.03	2.59
	9	1,820	1,340	143.3	138.3	44.8	8.72	8.10	0.14				
II	10	1,820					1,730	173.2	195.5	66.8	9.06						
	11	1,820					1,760	178.8	191.3	61.1	8.73			2.4	5.6	.96	2.85
	12	1,820	166.2	168.0	78.6	12.74	1,580	134.0	155.3	78.7	9.27	6.45	0.23				
	13	1,820					1,250	141.0	130.0	48.5	8.45						
III Compound E	14	1,820					2,040	209.7	235.9	106.8	10.28						
	15	1,820					1,200	82.2	118.3	73.7	9.70	7.00	0.52				
	16	1,820	166.4	168.1	80.8	13.40	1,320	100.6	123.8	62.8	9.40			6.2	8.3	1.10	2.48
	17	1,820					1,270	138.4	131.6	34.4	9.18	6.82	0.32				
IV Compound E	18	1,820					1,130	142.1	165.5	51.5	8.30						
	19	1,820					1,340	170.2	179.8	35.8	8.95	6.69	0.38				
	20	1,820	165.5	167.1	78.9	12.96	1,810	177.7	186.8	53.2	8.92			0.7	2.9	.43	1.26
	21	1,820					1,610	207.0	205.0	60.1	9.68	7.35	0.66				
V	22	1,820					1,700	186.3	188.7	59.5	9.09						
	23	1,820					1,510	174.2	182.7	60.4	8.60	6.31	0.46				
	24	1,820	165.0	168.5	83.4	13.70	2,010	220.4	220.4	76.2	9.90			1.1	6.1	1.09	3.60
	25	1,820					1,650	179.6	166.9	74.9	9.44	6.45	0.51				
	26	1,820					1,870	200.8	190.7	75.7	9.54						
	27	1,820					1,160	160.8	169.5	56.1	9.97	6.13	0.48				
													0.51				

This, however, was followed by an increase in weight, a decrease in urine volume, urinary sodium and chloride for several additional days only. Significant changes in hematocrit and serum protein levels did not develop but the serum urea nitrogen concentration decreased slightly.

A positive nitrogen balance was main-

during the final control period. There were reciprocal changes in serum potassium. As this subject developed twenty-four hours of generalized aches and slight fever the day following the conclusion of the final control period, it is not clear whether this alteration was related to the diuresis which commenced before the steroid was discontinued

or represented a metabolic change relating to the prodromas of an illness.

Compound E administration was associated with a fall in serum inorganic phosphorus concentration, again a slight decrease in total cholesterol, but no major change in

tolerance tests were uniformly conducted after a seventeen-hour fasting period. Daily analyses of the urine for reducing substances or ketone bodies were negative.

Determinations of radioactive iodine uptake,¹⁷ after the administration of 40 micro-

TABLE III(b)

Period	Hospital Day	Weight	"Resting" B.P.	E.S.R.	Hematocrit	W.B.C.	Neutrophils	Lymphocytes	Eosinophiles	Blood Sugar and Glucose Tolerance					
										Fast-ing	½ Hr.	1	2	3	4
		Kg.	Mm. Hg	Mm./hr.	% Cells	Cells/cu. mm.				Mg./100 cc.					
I	6	46.50	100/56	10	37.3	8,980	1,976	5,747	625	62					
	7	46.40	98/50												
	8	47.25	100/48												
	9	47.35	100/50	7,500	1,950	4,837	733	78	211	136	68	80	87
II	10	47.70	98/50	..	37.6										
	11	47.50	98/54												
	12	47.25	98/48												
	13	47.40	100/52	7,700	2,156	4,774	859	78	220	127	61	55	58
III Compound E	14	47.60	104/54	..	37.6	75					
	15	47.30	100/54												
	16	47.55	100/50												
	17	47.95	98/54	10,720	6,914	3,538	281	98	200	132	83	..	83
IV Compound E	18	48.20	104/54	..	36.7	89					
	19	48.45	106/50												
	20	48.80	112/56												
	21	48.55	106/60	10,535	7,322	2,844	234	83	200	147	69	76	81
V	22	48.20	108/60	15	37.3										
	23	48.05	116/64												
	24	48.10	114/60												
	25	47.70	112/58												
	26	47.85	114/60												
	27	47.30	104/66	..	42.8	77	250	132	80		
	33					7,700	2,926	3,927	806						

urinary 17-ketosteroid or "corticoid" excretion. The total stool fat¹⁶ was not modified significantly.

On the fourth and fifth day of treatment the fasting blood sugar levels were slightly higher than in other tests, and the blood sugar curves after intravenous glucose were minimally altered. No hypoglycemic reactions occurred at any time even though the

curies, were carried out eight days apart at the end of period II and IV; the uptake measured at twenty-four hours decreased from 23 to 14 per cent. The cardiac silhouette by x-ray increased very slightly following Compound E, and a slight elevation in the T waves was observed by electrocardiogram.

The "resting" blood pressure began to

rise after a few days of Compound E administration, peak values being reached just after the drug was discontinued.

CASE IV. M. S., a forty-six year old housewife, complained only of nervousness and weak-

were not reduced. X-ray of the heart disclosed moderate hypertrophy and the electrocardiogram showed left axis deviation and myocardial damage. Repeated urinalyses revealed variable glycosuria and two-plus albuminuria, together with occasional white blood cells; the urine con-

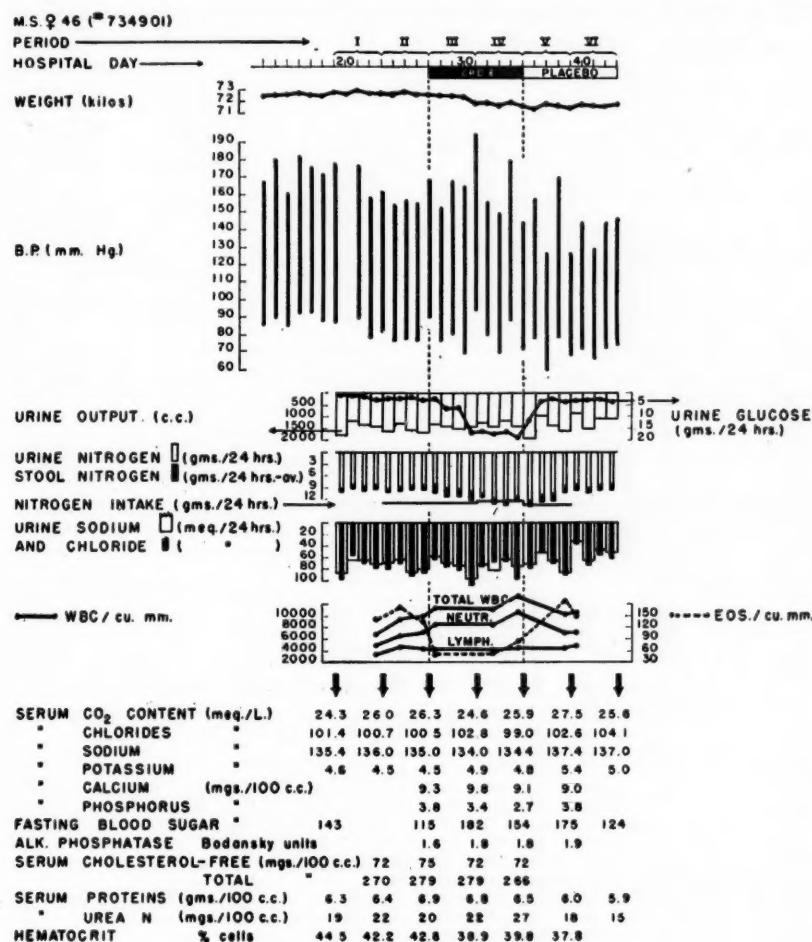


FIG. 4

ness when she was admitted after twenty-six years of known hypertension. Glycosuria with a fasting blood sugar of 152 mg. per 100 cc. was first noted five years before, initially controlled by diet alone and later supplemented by small doses of standard insulin. There was neither past nor present evidence of cardiac pain, congestive failure, cerebral disease or Cushing's syndrome. Physical examination was not remarkable except for a blood pressure of 230/110 and marked arteriolar changes, hemorrhages and exudate on funduscopic examination.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal arterial pressures

centrated to a specific gravity of 1.015; the phenolsulfonphthalein excretion was 80 per cent in two hours; and the intravenous pyelogram was normal. A benzodioxane test was negative.

The conditions of the experiment were identical with those described in the first patient. The diabetes was controlled satisfactorily with five units of standard insulin given daily before breakfast and at no time were there signs of acidosis, ketosis or insulin shock. No insulin was administered until the completion of the glucose tolerance test on the day when this procedure was undertaken. The diet employed in this patient contained 1,724 calories per day which included 70 Gm. of protein and 200 Gm. of

carbohydrate. Period I began on the nineteenth hospital day and Compound E (20 mg. intramuscularly at six-hour intervals) was administered for eight days. Placebo injections were given only during periods V and VI. The twenty-

dilution suggested slight retention. However, the urea nitrogen concentration rose during the periods of treatment.

Nitrogen balance studies indicated an increased excretion appearing soon after treat-

TABLE IV(a)

Period	Hos- pital	Intake					Urine							Stools			
		Fluid	Na	Cl	K	N	Vol- ume	Na	Cl	K	N	17-keto- steroids	"Corti- coids"	Na	K	N	Fat
		Cc.	mEq./24 hr.		Gm./24 hr.		Cc.	mEq.		Gm.		Mg./24 hr. (av.)		mEq./24 hr. (av.)		Gm./24 hr. (av.)	
I	19	1,690	1,670	87.2	99.0	66.8	9.16	2.15	0.77	4.4	9.8	0.98	3.0
	20	1,690	1,160	52.0	59.2	54.2	8.28						
	21	1,690	1,370	63.3	69.9	56.2	8.99						
	22	1,690	1,390	71.3	79.4	57.2	8.62						
II	23	1,690	1,570	70.0	79.8	62.5	9.28	1.21	0.87	4.9	6.5	1.03	1.6
	24	1,690	86.6	91.4	53.6	12.9	1,280	63.8	70.4	62.7	9.00						
	25	1,690	1,510	85.2	92.0	57.1	8.88						
	26	1,690	1,630	80.7	86.4	55.3	8.85						
III Com- pound E	27	1,690	1,300	59.0	61.8	57.6	8.02	4.80	0.98	6.9	21.2	2.11	2.9
	28	1,690	86.4	93.4	53.5	12.9	1,420	69.3	76.6	70.0	9.28						
	29	1,690	1,490	73.3	81.3	60.2	9.33						
	30	1,690	1,460	99.6	107.3	62.0	10.18						
IV Com- pound E	31	1,690	1,240	73.2	77.4	56.3	10.52	2.15	0.81	5.0	14.2	1.21	2.9
	32	1,690	83.1	90.5	50.6	12.5	1,430	81.4	67.2	63.2	12.06						
	33	1,690	1,160	65.4	67.2	57.1	12.32						
	34	1,690	1,370	77.9	95.3	41.8	11.60						
V	35	1,690	1,860	77.2	79.3	46.1	12.18	1.09	1.08	6.8	16.0	1.48	3.5
	36	1,690	84.3	91.2	57.7	13.2	970	53.8	57.3	42.3	11.08						
	37	1,690	1,360	64.0	70.7	51.0	10.80						
	38	1,690	1,530	86.2	87.0	48.5	8.94						
VI	39	1,690	850	32.7	37.7	61.7	8.59	0.92	1.08	6.5	13.7	1.40	3.8
	40	1,690	1,500	68.7	73.5	62.2	9.01						
	41	1,690	1,040	48.4	57.2	63.5	8.72						
	42	1,690	1,040	51.9	61.3	62.7	8.60						

four-hour urinary excretion of reducing substances was determined by Benedict's method.

Results. The results are shown in Figure 4 and Table IV. No subjective change was noted. Compound E (80 mg. daily) appeared to have minimal effects on water and salt metabolism. There was no increase in weight or significant change in urine volume but a transient decrease in urinary sodium and chloride as well as evidence of hemo-

ment began. Serum sodium concentration fell slightly together with reciprocal changes in serum potassium. Compound E administration was associated with a decrease in serum phosphorus concentration, a very slight decline in total cholesterol and possibly a small increase in 17-ketosteroid and "corticoid" excretion. The total stool fat was not modified significantly. Fasting blood sugar levels were higher during the period of steroid treatment. On the fourth day after

the start of Compound E the peak levels of blood sugar were higher than in other glucose tolerance tests, and the character of the curve was more abnormal on both tests conducted during the treatment pe-

show considerable fluctuation. Nevertheless, there was a suggestive increase in some readings during Compound E administration, followed by a decrease in average values after the drug was discontinued.

TABLE IV(b)

Pe- riod	Hos- pital Day	Weight	"Rest- ing" B.P.	Sed. Rate	Hemato- crit	W.B.C.	Neutro- philes	Lympho- cytes	Eosino- philes	Blood Sugar and Glucose Tolerance					
		Kg.	Mm. Hg	mm./ hr.	% Cells	Cells/cu. mm.				Fast- ing	½ hr.	1	2	3	4
I	19	72.90	178/86	30	44.5										
	20	72.81													
	21	73.00	176/90												
	22	72.86	158/78	5,000	3,125	1,750	44	116	...	270	198		
II	23	72.83	162/82	..	42.2										
	24	72.69	154/76	7,680	4,631	2,803	61	144	334	250			
	25	72.84	156/78												
	26	72.54	154/74	8,080	5,271	2,464	45	108	303	256	213	171	125
III Com- pound E	27	72.54	168/90	..	42.8	9,530	6,757	2,287	22						
	28	72.38	152/76												
	29	72.40	168/80												
	30	72.28	164/70	167	334	308	241	172	152
IV Com- pound E	31	71.87	194/94	..	38.9										
	32	71.91	156/80	9,150	6,771	2,104	28						
	33	71.69	150/70												
	34	71.95	180/88	11,480	8,830	2,411	57	167	278	242	228	222	189
V	35	71.65	144/72	35	39.8										
	36	71.36	158/78												
	37	71.79	126/60												
	38	71.64	170/78	8,290	5,389	2,518	156	137	294	227	184	163	127
VI	39	71.34	126/68	..	37.8	8,500	5,270	2,975	120						
	40	71.79	144/72												
	41	71.60	130/66												
	42	71.65	144/72												
	43	71.75	146/74												

riods. The total daily excretion of reducing substances was markedly increased in association with the drug administration. Daily urine samples throughout the experiment were negative for acetone and diacetic acid.

The sedimentation rate remained unaltered and teleroentgenograms and serial electrocardiograms were not modified.

Despite the usual baseline period, "resting" blood pressure values continued to

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COMMENT

It must be emphasized that the results obtained in this study represent short-term observations on a limited number of patients treated with 11-dehydro-17-hydroxy-corticosterone acetate.* It is not known whether Compound E, either free or esterified, con-

*Furnished through the courtesy of Merck and Co., Inc., Rahway, N. J., in the form of a suspension in peanut oil, each cc. containing 10 mg.

stitutes a hormone normally elaborated by the adrenal cortex. Furthermore, it is not known whether 80 mg. per day represents a small or a large dose, particularly since only a minute fraction of this dose appears in the urine as a "corticoid" as compared with the large amounts of "corticoid" material presumably elaborated by the adrenal cortex; moreover, there is the possibility of suppression of the patients' own adrenal cortical function by this steroid.

In all patients tested Compound E produced slight to moderate salt and water retention, usually with evidence of hemodilution. This was followed by a conspicuous diuresis in one subject. In the Addisonian patient on the first day of drug treatment this retention was preceded by a transitory increase in the excretion of water, sodium and chloride. In contrast to the familiar electrolyte effects of desoxycorticosterone acetate, the use of Compound E was associated with a small decline in serum sodium concentration of from 1.8 to 3.2 mEq. during the period of steroid administration.

With the dosage of Compound E employed no major changes in the excretion of potassium were evident. However, mention should be made of another patient with uncomplicated hypertensive vascular disease who received a daily dose of 150 mg. on two separate occasions. Although detailed studies were not undertaken, a transitory increase in potassium excretion of about 40 mEq. was noted during the first twenty-four hours, preceding the usual but transient retention of water or sodium. This phenomenon also occurred in the same patient upon the administration of adrenocorticotrophic hormone.

A negative nitrogen balance was observed in two patients, appearing only after a few days of Compound E treatment. A significant change was not apparent in the subject with Addison's disease. Despite the modification of carbohydrate metabolism the increased nitrogen excretion was not considered proof of increased conversion of protein to carbohydrate, although such a mechanism may be responsible.

In three of the four patients small in-

creases in fasting blood sugar and slight alterations in glucose tolerance curves were obtained during the course of Compound E therapy. The increase in twenty-four-hour excretion of reducing substances in the diabetic subject indicated that these changes were real. The fourth patient, a hypertensive treated for five days, showed no change in fasting blood sugar values. No glycosuria developed in the non-diabetic patients but traces of acetone appeared in two instances, limited to the fourth day of steroid administration. Although the excretion of reducing substances by the diabetic rose sharply, it must be recalled that small increases in blood sugar above renal threshold values would be sufficient to account for this degree of glycosuria and that the possible contribution of a change in threshold has not been investigated. In the non-diabetic patients the alterations in carbohydrate metabolism produced by Compound E were of small magnitude. In the one Addisonian patient studied the effect on the seventeen-hour fasting blood sugars and glucose tolerance curves would not justify the conclusion that this agent will prevent or modify the hypoglycemia with complete regularity in hypoadrenalism.

The rise in total white blood cell count and the fall in eosinophiles observed in three patients including the one with Addison's disease implies that Compound E may act directly on leukocytic mechanisms.

Small changes in "resting" blood pressure were apparent in all patients. These, however, were consistently greater than those observed in this clinic in control hypertensives treated with placebos and for similar periods of time. Whereas the arterial tension declined during or after therapy in the hypertensive subjects, it rose in the patient with adrenal cortical insufficiency more than would be expected on the basis of salt and water retention alone. It should be recalled that desoxycorticosterone acetate, which provokes comparable degrees of salt and water retention (but no reduction in serum sodium concentration), has been found to exhibit pressor properties when studied under similar conditions in hyper-

tensive patients.¹⁸ The difference in response of the Addisonian patient and the delayed effect on "resting" blood pressure in all subjects imply that Compound E has no direct humoral action. These observations supplement the results obtained with an adrenal cortical extract¹¹ and suggest that the drop in blood pressure produced by the extract may have been due to Compound E-like substances. If the rise in arterial tension observed in the patient with Addison's disease was not attributable to an increased blood volume, it is possible that this steroid requires the presence of an intact adrenal for its depressor effect and may act as a pressor agent in the absence of the adrenals.

CONCLUSIONS

1. Clinical and metabolic studies were undertaken in two patients with hypertensive vascular disease, one with Addison's disease, and one with hypertension and diabetes in order to determine the effects of 11-dehydro-17-hydroxy-corticosterone acetate (Compound E) administration in doses of 80 mg. daily.

2. Compound E induced small to moderate retention of salt and water, slight reductions in serum sodium concentration, inconstant negative nitrogen balance, small changes in carbohydrate metabolism (and, in two patients, transient acetonuria) and a drop in total cholesterol not at the expense of the free cholesterol.

3. An increase in circulating white blood cells, due primarily to polymorphonuclear leukocytes, together with a drop in eosinophiles, was recorded in three patients including the one with hypoadrenalism.

4. Compound E exerted a depressor effect on the "resting" blood pressure of the hypertensive patients and a rise in pressure in the Addisonian patient.

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Review

Role of the Neurohypophysis in the Pathogenesis of Hypertension and Some Allied Disorders Associated with Aging*

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THE frequency with which aging is accompanied by such disturbances as hypertension, arteriosclerosis, obesity, diabetes mellitus and sexual impotence suggests that these disturbances may reflect the gradual failure of some as yet unknown homeostatic mechanism. This paper assembles the evidence which supports the view that hypofunction of the neurohypophysis may represent a common pathogenetic denominator. It is written in full awareness that the theory to be set forth is far from proved but also in appreciation of the value of Charles Darwin's statement that "without hypothesis there can be no useful observation."

The present concept was first presented by Heinbecker¹⁻⁴ but his experiments and deductions are not as widely appreciated as they should be. We here present additional data from the literature which appears to be relevant.

CUSHING'S SYNDROME

A discussion of Cushing's syndrome affords a suitable point of departure. It is possible to accept the view that a patient with this disorder may simply be an unfortunate person in whom, for reasons to be discussed later, many of the ills which beset aging man are concentrated in unhappy intensity. This broad biologic viewpoint seems justified when one considers the chief manifestations separately. The classic fea-

tures are, of course, obesity, hypertension, arteriosclerosis, an insulin-resistant type of hyperglycemia, sexual impotence, osteoporosis, muscular weakness and frequently cancer. There are often other abnormalities as well but these seem to be the most important, and it is obvious that they are the very disorders which contribute so heavily to the morbidity and mortality of later life. It taxes credulity to assume that when all these disturbances are assembled in one person said then to have Cushing's syndrome, each of them has developed by a special mechanism not operating in individuals less spectacularly afflicted. There is no proof that any one of these features of Cushing's syndrome differs fundamentally from the same feature appearing much more commonly in the general population. It is tempting to conclude that when Cushing's syndrome is understood the most commonly and deadly afflictions of old age will also be understood and that in many persons there develops with increasing maturity one or more facets of this complex disorder which is so dramatic in its full-blown form.

The bodies of many persons with Cushing's syndrome contain tumors of one endocrine gland or another—the adrenal cortex most commonly—but also the anterior pituitary, thymus or ovary on occasion. Of those without tumor many have unmistakable hyperplasia of both adrenal

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cortices. Still others have shown no gross abnormality whatever of any endocrine gland.⁵ The only common denominator thus far demonstrated which links all these cases together is the peculiar hyalinization of the basophilic cells in the anterior pituitary described by Crooke⁶ and accepted by others.⁷⁻⁹ Although opinion¹⁰ is not unanimous concerning the specificity of these cellular changes, it appears to be nearly so, and it is therefore mandatory that the origin and significance of these Crooke cells be explained since they seem to represent the key to the problem.

The only clue yet to appear comes from the study of that especially intriguing group of cases with no evidence of endocrine tumor or adrenocortical hyperplasia, and here again another apparent common denominator has recently been described. Influenced by previous studies on dogs which showed that destruction of certain hypothalamic nuclei causes obesity and other changes reminiscent of Cushing's syndrome,¹¹ Heinbecker¹ reported that four such patients showed atrophy of the paraventricular nuclei in association with Crooke cells; a fifth patient with cancer of the adrenal cortex had Crooke cells but normal hypothalamic nuclei. The idea was then propounded that the integrity of the basophiles and their respective end organs is dependent upon hormones issuing from the neurohypophysis, and that depression of basophilic function results in relative hyperfunction of the pituitary eosinophiles and their respective end organs. Basophilic hypo-activity can be induced either by any neurologic event which inhibits the function of the neurohypophysis or, more commonly perhaps, by the formation in excessive amounts of other hormones physiologically antagonistic to those of the neurohypophysis. The basic observation concerning the effect of hypothalamic lesions upon the structure and function of the anterior pituitary has not yet been confirmed but an attempt will be made here to see if available collateral evidence can be interpreted in favor of this doctrine.

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EFFECTS OF HYPOTHALAMIC LESIONS

Information concerning the effects of hypothalamic lesions upon homeostasis is meager, but enough is available to justify the suspicion that the neurohypophysis may be an important regulator of the processes under discussion.

Obesity. Without questioning in the least the demonstration by Newburgh¹² and Conn¹³ that the same thermodynamic relations exist in obese as in normal persons, it seems possible to suggest that qualitative metabolic differences may exist within a normal quantitative frame. No one questions the fact that the obesity in Cushing's syndrome associated with adrenocortical tumor or hyperplasia is promoted by hormones emanating from that gland; indeed Albright¹⁴ has postulated that the fundamental defect in these forms of Cushing's syndrome is the overproduction of adrenocortical hormones which promote the formation of glucose from protein and suppress the peripheral oxidation of glucose. The present theory suggests that a state of relative hyperadrenocorticism exists when basophilic function is depressed and eosinophilic function is therefore unopposed. Or, conversely, it may be said that hypofunction of the neurohypophysis and its dependent basophiles may sensitize the organism to adrenocortical hormones in such a way as to promote the storage of fat.

The development of obesity in animals with hypothalamic lesions has recently been reviewed by Brobeck.¹⁵ The most effective lesions involve the ventromedial nuclei and they cause gain in weight chiefly by increasing appetite and diminishing physical activity. Striking gain or loss of weight is commonly seen clinically in association with lesions in this area of the brain. It appears that concomitant injury to the anterior pituitary is not a factor.¹⁶

Histologic observations in simple obesity are scarce but there are some which suggest the co-existence of basophilic degeneration. Ranson and associates¹⁷ produced adiposity and diabetes mellitus in a monkey with

bilateral hypothalamic lesions and Rasmussen¹⁸ noted basophilia in its anterior pituitary. In a review of the literature Goldzieher¹⁹ found that basophilia was a common but not constant anatomic change; he also reported ten cases of obesity with increased numbers of basophiles and chromophobes and nine control patients without such disproportions. Heinbecker⁴ has produced basophilic degeneration by denervation of the neurohypophysis and increased the number of basophiles by administering pitressin. Failure to demonstrate histologic abnormalities in the hypothalamus and pituitary²⁰ does not, of course, preclude the possibility of functional depression of neurohypophyseal activity or of hormonal counterbalance in peripheral tissue.

There is also evidence, equivocal and unconvincing as it may be at the present, that pituitrin itself modifies fat metabolism. Several studies have shown the capacity of this hormone to produce fatty infiltration of the liver, presumably by transferring fat from other depots²¹⁻²⁵ although the existence of a separate hormone "lipuitrin"²⁵ has not been confirmed. Van Dyke²⁶ stated that extracts of the posterior pituitary probably do not significantly affect the concentration of cholesterol and phosphatides in the blood of normal mammals. Blotner²⁷ observed this to be true in normal humans but claimed that pituitrin abolishes alimentary hyperlipemia in patients with obesity or diabetes insipidus.

In view of the constancy with which most young people maintain their body weight in absolute conscious disregard of caloric intake or energy output and the almost universal tendency of older people to become heavier, it seems reasonable to suppose that obesity is not always a matter of gluttony or sloth. It is here suggested that subtle changes in the metabolic mixture occur as age produces diminished secretions of adrenocortical antagonists.

Diabetes Mellitus. The capacity of the eosinophile-adrenocortical complex to induce an insulin-resistant type of hyperglycemia is demonstrated clinically by its

frequent occurrence in acromegaly and in Cushing's syndrome, and experimentally by Heinbecker and Rolf's²⁸ demonstrations that insulin sensitivity is greatly increased when eosinophilic function is impaired. Heinbecker² has furthermore shown that denervation of the neurohypophysis increases the resistance of dogs to the effects of insulin. Histologic evidence of eosinophilic proliferation in human diabetes mellitus has been both denied²⁹ and reported.³⁰⁻³¹ The amelioration of pancreatic diabetes by hypophysectomy or adrenalectomy is, of course, well known as is the insulin-sensitivity of patients with Simmonds' disease.

Destructive lesions in the hypothalamus are known to modify carbohydrate metabolism but the results are difficult to interpret because of possible concomitant injury to the anterior lobe and because the nerve supply to the liver, adrenals and pancreas may also be disturbed. Chronic hyperglycemia has, however, occasionally been produced in animals by lesions involving the lateral nuclei^{17,33,34} and Morgan and associates³⁵ described atrophy of the paraventricular nuclei in each of fifteen cases of clinical diabetes mellitus. Carbohydrate tolerance diminishes with age.³⁶

The hyperglycemic action of pituitrin is apparently inconsistent with this general thesis but the mechanism of this action is not at all understood.³⁷ It must be admitted that no reports have been found which suggest that neurohypophyseal extracts have an insulin-like action.

Diabetes Insipidus. Of all the hypothalamic functions that of control of water metabolism is perhaps the best understood. There appears to be almost universal agreement that the integrity of the supra-opticohypophyseal tract is necessary if enough antidiuretic hormone is to be elaborated by the neurohypophysis to permit the renal tubules to absorb proper amounts of glomerular filtrate.^{38,39} Destruction of this same tract is not the only important factor, however, for the control of water balance also depends upon the

action of the adrenal cortex.^{40,41} Adrenalectomy greatly reduces the fluid exchange in cats with diabetes insipidus and pitressin prolongs the lives of adrenalectomized cats with diabetes insipidus.⁴² The prolonged water diuresis of humans with diabetes insipidus⁴³ resembles that seen in adrenal insufficiency.⁴⁴ Gersh and Grollman⁴⁵ noted no anatomic changes in the neurohypophyses of rats dead of adrenal insufficiency but Martin and associates⁴⁶ claimed that hyperfunction of the posterior pituitary follows adrenalectomy. From a clinical point of view the combination of hypopitressinemia and relative hyperadrenocorticism might well explain the low grade polyuria of elderly persons who have no abnormalities of the lower urinary tract, as well as that so often seen in diabetes mellitus, obesity and Cushing's syndrome.

Gonadal Failure. The association between hypothalamic lesions and hypogonadism, long recognized clinically, has recently been reviewed by Bard.⁴⁷ Dey⁴⁸ reported that genital atrophy is caused by lesions involving the median eminence whereas injury to the anterior hypothalamus produces genital hypertrophy and pronounced ovarian follicular development due to lack of luteinizing hormones. Brooks⁴⁹ believed that there are enough nerve pathways between the hypothalamus and the anterior pituitary to justify the assumption that the output of gonadotrophic hormone is at least in part regulated by the central nervous system, a viewpoint strengthened by the demonstration⁵⁰ that section of the pituitary stalk has a definite effect upon the estrous cycle of guinea pigs. Heinbecker¹ attributed gonadal failure to loss of basophilic function. By comparing the changes in dogs produced by denervation of the neurohypophysis with those following total hypophysectomy (the median eminence is also destroyed), he found that the basophiles are trophic to the thyroid, the follicular cells of the ovary and the sperm cells of the male. Confirmation of these observations might then explain the frequent association of gonadal failure with obesity, diabetes mellitus,

"menopausal hypertension" and Cushing's syndrome. It might also account for the relatively high incidence of hypometabolism and hypercholesterolemia in these conditions. Gonadal failure is often associated with experimental⁵¹ and clinical⁵² diabetes mellitus.

Osteoporosis. Albright⁵³ has recently reviewed his studies which show that some forms of osteoporosis are associated with disturbances in the metabolism of protein rather than with defects in the ability of the body to handle minerals. In Cushing's syndrome and other diseases of adaptation osteoporosis is attributed to excess of these adrenocortical hormones which accelerate gluconeogenesis; in old age loss of gonadal hormones and excess of adrenocortical "N-hormone" appear to be important. Regardless of the precise mechanism, hyperadrenocorticism—absolute or relative—is obviously a fundamental contributing factor in the common types of skeletal demineralization.

Blood Pressure. It remains to inquire whether a similar approach may not clarify the pathogenesis of chronic diastolic hypertension. A satisfactory theory concerning the pathogenesis of hypertension must take into account the following factors: (1) Genetic variations which make one person's blood vessels more susceptible than another's to stimulation and disease; (2) psychogenic influences which result in personality disorders; (3) lack of evidence for increased sympathetic tone in at least the majority of patients with essential hypertension; (4) the remarkable similarity between experimental renal and clinical essential hypertension; (5) the tendency of "renal" hypertension to assume a chronic "non-renal" form; (6) the probable causal relationship between hyperadrenocorticism and the diseases of adaptation; (7) frequent association of high blood pressure with old age, arteriosclerosis, obesity, hyperglycemia, hypercholesterolemia, sexual impotence, polyuria, osteoporosis, pregnancy, renal diseases and benign prostatic hypertrophy.

To date, the chief obstacle to acceptance

of the humoral origin of hypertension is the consistent failure of many workers to demonstrate increased amounts of pressor materials in biologic fluids of animals and humans with chronic hypertension.⁵⁴ Negative hormone assays, however, do not exclude the possibility that the organism has become sensitized to normal amounts of circulating pressor substances, and the essence of the present theory is that appropriate lesions in the hypothalamus create this condition of relative pressor excess by diminishing the production of antipressor substance. More specifically, it is postulated that destruction of the paraventricular and supra-optic nuclei and the consequent depression of neurohypophyseal activity so alters the eosinophile-basophile activity ratio of the anterior lobe as to create a state of heightened tissue responsiveness to the combined actions of such pressor materials as desoxycorticosterone, progesterone, renin and epinephrine. If this is true, then the fact that essential hypertension is often not accompanied by demonstrable overproduction of specific steroids,⁵⁵⁻⁵⁷ renin⁵⁸ and epinephrine,⁵⁹ loses force. There is at the present time much suspicion but no proof that dysfunction of the adrenal cortex exists in essential hypertension. Gross pathologic observations have been of little value. Claims have been made that hyperplastic and adenomatous changes in the adrenal cortex occur with significant frequency in hypertension and diabetes mellitus⁶⁰⁻⁶⁴ although the evidence to the contrary seems more convincing.^{56, 65-67} Histologic studies have been equally inconclusive although a systematic application of the Ponceau fuchsin reaction is obviously needed.⁶⁸ The physiologic approach has been somewhat more productive, particularly the demonstration by Selye^{70, 71} and others⁷² that certain steroid hormones can under certain conditions cause hypertension and various vascular lesions. Obliteration of experimental renal hypertension by adrenalectomy and its re-appearance following substitution therapy has been amply confirmed;^{73, 74} Selye⁵⁷ reported that some patients with es-

sential hypertension exhibit the high serum $\frac{\text{Na}}{\text{Cl}}$ ratio reminiscent of Cushing's syndrome. Knowlton and co-workers⁷⁵ showed that hypersensitivity to desoxycorticosterone acetate and sodium also exists in rats with serum-induced nephritis. Perera⁷⁶ reported the case of a man with established hypertension whose blood pressure dropped with the onset of Addison's disease and increased under the influence of desoxycorticosterone acetate; he⁷⁷ showed that hypertensive humans withstand salt deprivation much more easily than normal subjects do and that sodium potentiates the pressor activity of desoxycorticosterone acetate in hypertensive subjects,⁷⁸ and, importantly from the standpoint of the present thesis, he⁷⁹ claimed that patients with essential hypertension are hypersensitive to the pressor action of desoxycorticosterone acetate. In later papers, however, he^{79a and 79b} reported that this response gradually disappears despite continued administration of this steroid and that desoxycorticosterone glucoside and adrenal cortical extract have no pressor activity in hypertensive humans. Goldman and Schroeder^{79c} also reported that hypertensive humans are abnormally sensitive to the blood pressure-raising action of DOCA but that propylene glycol, adrenal cortical extract, progesterone, testosterone, dehydroisoandrosterone acetate, Δ^5 pregnenolone and 17-hydroxy-11-dehydrocorticosterone had no such pressor activity when given intravenously. An obvious contrast can, of course, be made between the hypertension of Cushing's syndrome and the hypotension of Addison's disease, and the present interest in sodium depletion as a method of treating high blood pressure testifies to the probable alterations in adrenocortical function.⁸⁰

Any experimental method which will induce eosinophilia of the anterior pituitary, therefore, assumes prime importance for these cells appear to be trophic to the adrenal cortex. The validity of this concept and its associated implications rests solely upon the unconfirmed experiences of Heinbecker¹⁻⁴ with three different types of

neurosurgical procedures illustrated diagrammatically in Figure 1. Simple hypophysectomy (A) is functionally equivalent to anterior lobectomy since the median eminence and part of the stalk remain as sources of neurohypophyseal hormone. Total

hypophysectomized (operation B) leads to the further conclusion that the eosinophiles, on the other hand, are trophic to the heart, renal tubules, adrenal cortex, corpus luteum, the cells of Leydig and the prostate. These organs do not atrophy following denerva-

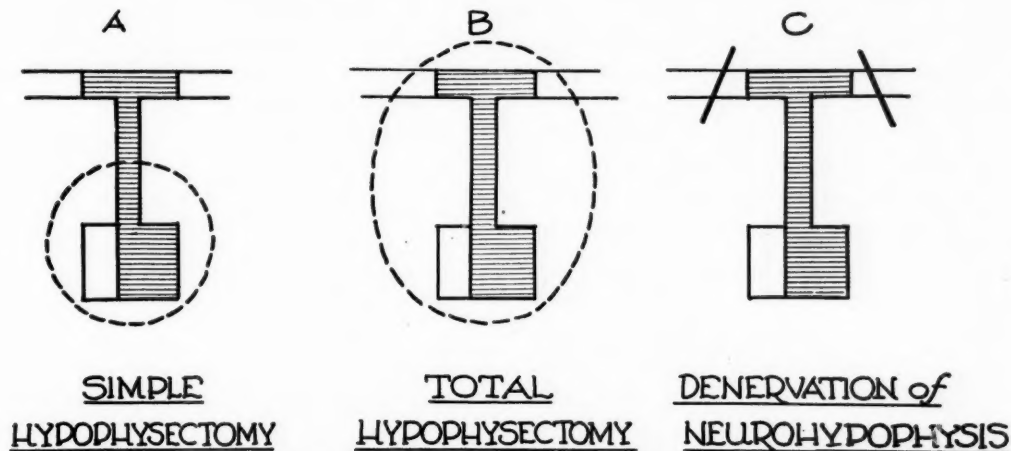


FIG. 1. Heinbecker's technic for separating the eosinophilic and basophilic functions of the anterior pituitary. Operation C produces only basophilic degeneration.

hypophysectomy (B) represents excision of all anterior and posterior lobe tissue. Denervation of the neurohypophysis by appropriate incisions in the anterior and posterior hypothalamus (C) is functionally equivalent to neurohypophysectomy since all pituitrin-forming tissue is inactivated without concomitant damage to the anterior lobe. Heinbecker's fundamental contribution consists of his demonstration that in dogs operation C is followed, after a latent period of a few months, by profound histologic and physiologic changes in the anterior pituitary. Such preparations⁴ show not only a large reduction in the number of basophiles but also degenerative changes in the few which remain; the anterior lobe consists almost entirely of eosinophiles and chromophobes with only a sprinkling of degranulated turbid basophilic elements. Since these animals also show regressive changes in the thyroid, follicular cells in the ovary and the sperm cells in the male, it is furthermore assumed that hormones from the basophiles are trophic to these glands. Comparison of these observations at autopsy with those in animals totally

tion of the neurohypophysis with its attendant basophilic degeneration nor does this operation modify the hypertrophy of the remaining kidney or adrenal in such animals which are also unilaterally nephrectomized or unilaterally adrenalectomized. The importance of the pituitary eosinophiles in the regulation of the circulation is shown by the extremely high urea clearance in acromegaly⁸¹ and by the profound reduction in arterial pressure, cardiac output, renal blood flow and diodrast-Tm which follows simple or total hypophysectomy but not denervation of the neurohypophysis.^{3,82,83} Growth may be largely a function of blood flow.

Confirmation of these claims is urgently needed for they possess startling implications. Some of these are: (1) a correlation between cellular structure and function in the anterior pituitary exists which is not now generally conceded; (2) the growth and integrity of the basophiles depend upon humoral agents elaborated by the neurohypophysis; (3) hypofunction of the neurohypophysis sensitizes the organism to adrenocortical hormones and possibly to other

pressor substances as well and (4) the eosinophiles exert a profound effect upon the circulation.

Figure 2 shows schematically how hypothalamic lesions may produce basophilic degeneration with its attendant suppression

not been specifically repeated, supportive evidence is available from other sources. Mellgren's⁶⁸ quantitative studies of the cellular changes in the anterior pituitary and adrenal cortex in Cushing's syndrome and allied diseases are in accord although

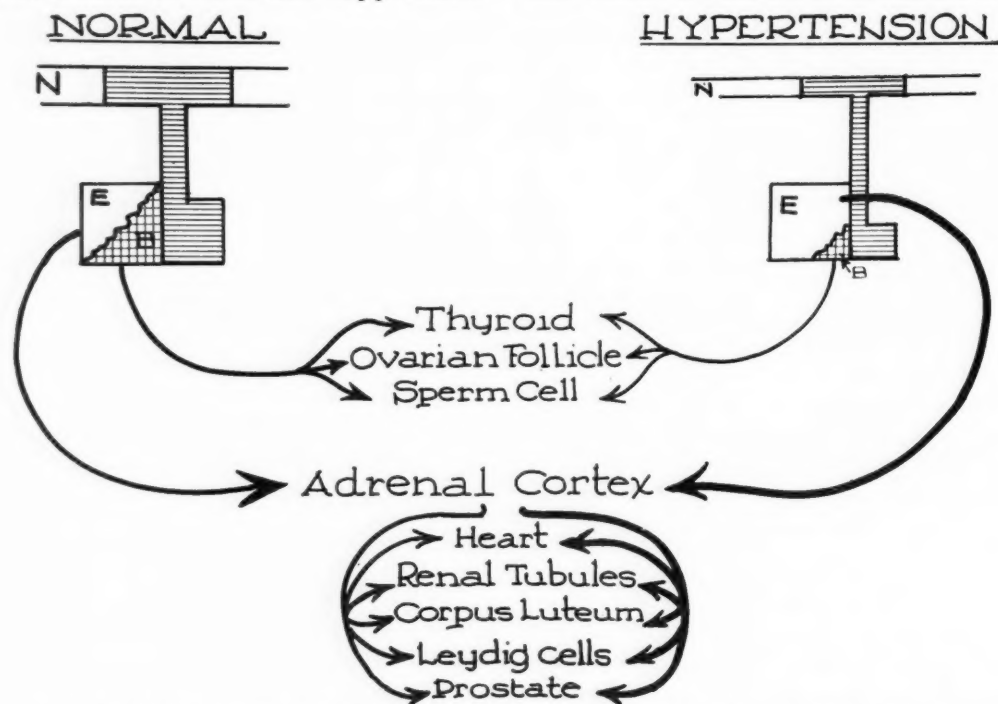


FIG. 2. Heinbecker's concept of the manner by which hypofunction of the neurohypophysis and degeneration of the anterior lobe basophiles result in relative hyperadrenocorticism.

of thyroid and gonadal function on the one hand and eosinophilic dominance with subsequent hyperactivity of the adrenal cortex and its various target organs on the other hand. If valid, the concept means that Cushing's syndrome, of which hypertension is a fundamental feature, can be produced by:

1. *Overproduction of Steroid Hormones.* This obviously accounts for the hypertension in those cases of Cushing's syndrome caused by tumor or hyperplasia of the adrenal cortex. For some unknown reason adrenocortical hyperplasia apparently also accompanies arrhenoblastoma⁸⁴ and cancer of the thymus.^{85, 86} In these cases no hypothalamic lesion need be postulated; the Croke changes are due to neutralization of neurohypophyseal hormone by excessive corticoid.

2. *Destructive Lesions in the Hypothalamus.* Although Heinbecker's experiments have

his interpretations are at variance with those here offered. Without comment on the mechanism of the results obtained by Sevringhaus and Thompson,⁸⁷ it may be noted that they produced in a different manner the same combination of Croke cells and atrophy of the thyroid and gonads. Chronic hydrocephalus might be expected to initiate such a mechanism; Heinbecker⁴ reported dramatic reversal of Cushing's syndrome in one case following removal of a meningioma from the foramen magnum, and Kraus⁸⁸ reported basophilic degeneration and adrenocortical hypertrophy in a series of patients with lesions in the region of the third ventricle. Rasmussen⁷ observed a rough correlation between basophilia and the age of the patient, a hint that nuclear abiotrophy might be the common denominator. Heinbecker⁴ conversely reported that administration of

large amounts of pituitrin in normal dogs leads to basophilic proliferation. It is at least conceivable that increased intracranial pressure may occasionally be the cause of malignant hypertension rather than the result.

The fact that denervation of the neurohypophysis in dogs (operation c) did not result in severe and sustained hypertension¹ appears to offer a serious objection to the present theory, as is also the fact that no correlation between diabetes insipidus and hypertension has been described. In Heinbecker's³ series of patients with diabetes insipidus, however, a relatively high incidence of moderate hypertension was reported, and in our small series⁸⁹ of five patients three had blood pressures definitely higher than 140 diastolic and 90 systolic. It seems likely, however, that the paraventricular nuclei are more important than the supraoptic group from the standpoint of Cushing's syndrome; in addition to the evidence already cited, Sattler and Ingram⁹⁰ reported that section of the supraopticohypophyseal tracts high in the median eminence of dogs with renal hypertension results in a decline of blood pressure, and DeBodo and Marine⁹¹ noted no endocrine abnormalities in dogs made polyuric by section of the same tract. Walter and Pijoan,⁹² on the other hand, produced severe and sustained hypertension in one dog by a small incision made transversely in the hypothalamus immediately posterior to the infundibulum.

3. *Functional Inhibition of the Neurohypophysis.* Perversion of function is not necessarily reflected in distortion of structure so that histologic evidence of eosinophile-adrenocortical dominance need not be demanded. Sustained cerebrocortical inhibition of hypothalamic nuclei in a person whose blood vessels are genetically predisposed to pressor stimuli must be a common combination. "Hypopituitrinemia"—a term to describe underproduction of neurohypophyseal hormones, known or unknown—may be of any grade and is probably seldom so complete as to raise

compensatory endocrine changes to the visual threshold. It usually requires half a lifetime for hypertension to develop. Afferent pathways to the hypothalamic nuclei are known to be widespread⁹³ but impulses from the frontal lobe are apt to be of special importance in the etiology of diseases of adaptation.

Arteriosclerosis. The experimental production of vascular lesions by adrenocortical substances⁷⁰ offers an important clue concerning the etiology of this common condition, and the deposition of cholesterol in atheromatous lesions suggests, of course, that disturbances in steroid metabolism are contributing factors.

Old Age. No studies concerning the effect of age upon the structure of the hypothalamus have been found, but Rasmussen⁷ observed increasing basophilia. The "adrenopause" comes later than the "menopause,"⁵³ a fact which may have some bearing upon the acknowledged correlation of the disorders under discussion with increasing maturity or decay.

PITUITRIN ANTAGONISTS

If it be claimed that hypofunction of the neurohypophysis sensitizes the organism to pressor substances elaborated by the adrenal cortex, the kidney and other organs, it must be demonstrated that pituitrin is capable of neutralizing, at least in part, the action of certain known hormones.

Desoxycorticosterone Acetate (DOCA). It is not claimed that the effects of this hormone on salt and water metabolism are restricted to the neutralization of pitressin but, when given to normal animals in large amounts, DOCA produces a state of chronic polyuria similar in many ways to diabetes insipidus^{40, 82, 94} but differing from it in that it is relatively unresponsive to pitressin. Corey and Britton⁹⁵ observed that administration of DOCA to rats caused polydipsia, polyuria and reduced urinary excretory rates of sodium and chloride; the opposite effects were produced by pituitrin and when the two drugs were given together the action of pituitrin predominated. Zierler

and Lilienthal⁹⁶ produced in a man polyuria and polydipsia with DOCA. The ability of this substance to facilitate the re-absorption of sodium and water by the renal tubules is, of course, well known⁹⁷ and Shannon⁴¹ attributes the capacity of dogs with diabetes insipidus to maintain blood volume during dehydration to maximal tubular re-absorption of sodium occasioned by pituitrin deficiency. The opposing effects of adrenocortical extract or DOCA and pitressin upon the renal excretion of minerals have also been emphasized by Anderson and Murlin⁹⁸ and McQuarrie and co-workers.⁹⁹ Winter and co-workers¹⁰⁰ showed that adrenalectomy in cats with diabetes insipidus is followed by the usual rise in serum potassium concentration but not by any consistent decrease in serum sodium or chloride. A complete review of this subject is beyond the scope of this paper but additional references¹⁰⁰⁻¹⁰⁵ are offered which suggest but do not prove the existence of neurohypophyseal-adrenocortical antagonism. Possible antagonistic effects of pituitrin upon other functions of the adrenal cortex seem not to have been studied in detail although it is reported⁴² that pitressin does not prolong the life of the adrenalectomized cat. However, the suggestion of Corey and Britton⁹⁵ that excess of pituitrin might cause a syndrome resembling adrenocortical insufficiency is quite in harmony with the Heinbecker hypothesis. Evidence that DOCA can cause sustained hypertension in normal animals¹⁰⁶⁻¹¹⁰ has not been universally confirmed.^{111,112}

Denervation of the neurohypophysis in dogs sensitizes the renal blood vessels to the constrictive action of DOCA.^{82,113} Perera and Blood⁷⁸ showed that humans with essential hypertension respond in an exaggerated manner to the pressor activity of DOCA given subcutaneously, and Goldman and Schroeder^{79c,114,115} have also observed this phenomenon following intravenous administration.

Progesterone. No specific studies concerning the effect of pituitrin on the actions of progesterone have been found but this

steroid is closely related chemically and physiologically to DOCA. It is known at least that the lives of adrenalectomized animals are prolonged by crystalline progesterone¹¹⁶ and by pregnancy.¹¹⁷ Reynolds and Allen¹¹⁸ reported that progesterone neutralizes the *in vitro* action of pituitrin on estrogen-primed uterine muscle. Goldman and Schroeder^{79c,114,115} have published conflicting claims concerning the acute pressor response of hypertensive humans to intravenously administered progesterone dissolved in propylene glycol. Progesterone induces hypertension in normal animals.^{108,110,119-121}

Renin. Antagonism between the posterior pituitary and the kidney may be suspected from the fact that administration of renin produces chronic polyuria¹²² and Oster and Martinez¹²³ reported polydipsia and polyuria in rats with renal hypertension. Frankel and Wakerlin,¹²⁴ however, observed that renal hypertension in dogs does not modify the output of antidiuretic substance in response to hydration and dehydration.

Heinbecker⁴ produced chronic hypertension and eosinophilia of the anterior pituitary in normal dogs by wrapping the kidneys in silk but when the same procedure was applied to animals whose neurohypophysis had been previously denervated, death rapidly ensued in a manner resembling that which Goldblatt¹²⁵ described after extreme constriction of the renal arteries. Animals with experimental renal hypertension are reported to be hypersensitive to renin¹²⁶⁻¹²⁸ but the data are not convincing. Pitressin is said to diminish the pressor action of angiotonin¹²⁹ but its effect upon renin has apparently not been reported. Failure of posterior hypophysectomy¹³⁰ or of section of supra-optico-hypophyseal tract⁹⁰ to intensify renal hypertension may have been due to incomplete removal or inactivation of neurohypophyseal tissue. The matter of hypersensitivity of hypertensive man to renin and angiotonin has not been reported.

Epinephrine. Increased sensitivity to epinephrine has been reported in hyper-

tensive animals¹³¹⁻¹³³ and man¹³⁴⁻¹³⁷ but these results should be interpreted with caution since hypertensive subjects often appear to hyper-react to a variety of stimuli. Epinephrine does, however, greatly intensify the vasoconstrictive properties of certain proteins derived from various tissues, including the kidney,¹³⁸ and it is a substance capable of stimulating the formation of adrenotrophic hormone.¹³⁹

COMMENTS

The present hypothesis has many attractive aspects. It assigns to the central nervous system the important role in the pathogenesis of hypertension and allied diseases which it deserves. Heretofore, the vasomotor centers have received consideration because of the great importance of the adrenergic system in the adjustment of the organism to emergency situations, but there is no convincing evidence that sympathetic tone is increased in chronic essential hypertension.^{140-142a} The shifting of emphasis from the medulla oblongata to the more ancient structures comprising the floor of the third ventricle opens a new approach to the study of the aging process, which should appeal to students of psychosomatic medicine who have long been aware of the disastrous effects which chronic friction between the personality and its environment may exert upon the cardiovascular system.¹⁴³⁻¹⁴⁵ One would like to find anatomic evidence of hypothalamic disease and basophilic degeneration in all cases of continued diastolic hypertension but Rasmussen⁷ was unable to do so. No structural changes may be anticipated, however, if one assumes that chronic hypopituitrinemia can be produced in constitutionally susceptible persons by sustained inhibition of the hypothalamus from impulses arising from centers higher in the brain.

This theory accounts for the fact that no chemical evidence of increased hormonal production is usually found as strong hints exist that neurohypophyseal extracts antagonize several important pressor hormones. Cerebral abiotrophy with dimin-

ished secretion of the only hormone the brain is known to produce seems to be a logical event in the aging process, and this deficiency brings with it a state of *relative* hyperadrenocorticism. Heinbecker⁴ even reported that denervation of the neurohypophysis produces lymphopenia, a consistent accompaniment of certain forms of adrenocortical hyperfunction. Eosinophilic dominance may also be produced by the action of large amounts of DOCA,⁷ progesterone and renin^{4,146} although the "endocrine kidney" of Selye⁷¹ seems to secrete an antirenotrophic substance. Special types of hypertension, of course, are apt to appear in younger persons when overproduction of pituitrin-antagonists occurs with primary diseases of the adrenal cortex and kidney and in pregnancy, but the fundamental mechanism may be the same.

This hypothesis may explain the fact that hypertension of purely renal origin eventually becomes non-renal in nature,¹⁴⁷ the experimental observations being supported by clinical experience that nephrectomy seldom modifies the hypertension associated with unilateral renal disease unless the operation is done early. Significant amounts of renin have been observed in the blood of animals and man only in the early stages of hypertension or in acute disturbances of renal blood flow,^{148,149} so it appears that in established hypertension the need for excessive renin formation no longer exists. Heinbecker³ considers that renin production increases whenever the integrity of renal tubular tissue is threatened by disease or anoxia; the hypertension which it produces by constriction of extrarenal blood vessels is a compensatory phenomenon designed to maintain renal blood flow and glomerular filtration rate, and it is sustained by the neurohormonal mechanism herein described. If so, this compensatory effort performs its task at great expense to extrarenal organs and eventually destroys the kidney itself by producing vascular lesions. It is much too early to attempt a correlation between these views and those offered by Shorr and co-work-

ers^{150,151} concerning the importance of vaso-active materials from the kidney and liver in the regulation of the circulation.

This theory accounts for the acknowledged frequency with which hypertension and arteriosclerosis are associated with obesity, hyperglycemia, hypercholesterolemia, gonadal failure, osteoporosis and polyuria. There is also reason to suspect that benign prostatic hypertrophy and hyperostosis frontalis interna are also variants of the same underlying disorder.⁶⁸

Finally, this theory suggests that preventive and therapeutic measures may be achieved through substitution therapy. Hypertension has been treated with pituitrin before¹⁵² but for precisely opposing reasons to those herein advocated. One should note that for every disorder known to be associated with hyperfunction of some phase of adrenocortical activity, an analogue seems to have been produced by destructive lesions involving the hypothalamus and its appendage. If this concept appears to violate the laws of endocrine homeostasis, it may be argued that the diseases under discussion are themselves expressions of disturbed homeostasis. In any event it offers a fertile field for further investigation.

SUMMARY

Evidence, derived largely from Heinbecker's experimental investigations, is assembled to support the view that hypertension and many allied disorders of aging are due to hypofunction of the neurohypophysis. Diminished secretion by this gland results in degeneration of the basophiles of the anterior pituitary and their respective target organs and in a state of increased tissue sensitivity to the combined action of various pressor hormones.

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ADDENDUM

Additional pertinent references have appeared. By an entirely different technic Keller (KELLER, A. D. Experience in attempting to elucidate certain of the multitudinous functions of the pituitary gland,

using the experimental surgical approach. *Texas Rep. Biol. & Med.*, 6: 275, 1948) secured evidence that total hypophysectomy is not followed by adrenocortical atrophy if the hypothalamus is also injured and suggested that the hypothalamus creates a "contra-adrenotropic" hormone. Further evidence that the neurohypophysis and the adrenal cortex act in opposing directions is supplied by the report that adrenalectomy increases the concentration of antidiuretic substance in the blood of rats (BIRNIE, J. H., JENKINS, ROSEMARY, EVERSOLE, W. J. and GAUNT, R. An antidiuretic substance in the blood of normal and adrenalectomized rats. *Proc. Soc. Exper. Biol. & Med.*, 70: 83, 1949). Shaken and Greene (SHAKEN, J. G. and GREEN, D. M. Mechanisms of desoxycorticosterone action, relationship of fluid intake and pressor responses to output of antidiuretic factor. *Am. J. Physiol.*, 155: 290, 1948) found that DOCA given subcutaneously to rats caused polydipsia, hypertension and increased output of antidiuretic substance in the urine. Friedman and co-workers (FRIEDMAN, S. M., POLLEY, J. R. and FRIEDMAN, C. L. The effect of desoxycorticosterone acetate on blood pressure, renal function and electrolyte pattern in the intact rat. *J. Exper. Med.*, 87: 329, 1948) reported that DOCA pellets implanted in normal rats produced hypertension, constriction of efferent glomerular arterioles and a rise in plasma sodium. Patients with essential hypertension are hypersensitive to nor-epinephrine (GOLDENBERG, M., PINES, K. L., BALDWIN, ELEANOR DE F., GREENE, D. F. and ROH, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.*, 5: 792, 1948).

Seminars on Antibiotics

Origin and Nature of Antibiotics*

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ANTIBIOTICS are chemical substances which are produced by micro-organisms and which have the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms. They are characterized by certain

upon true fungi; others attack both fungi and bacteria; still others act only upon fungi. Some are also active against rickettsiae and a few of the larger viruses. Some antibiotics possess antiprotozoan activities, affecting trypanosomes or trichomonads.

TABLE I
TYPICAL ANTIBACTERIAL SPECTRA OF SEVERAL ANTIBIOTICS—UNITS OF ACTIVITY PER 1 GM.
OF PREPARATION

Test Organism	Penicillin *	Actinomycin	Streptomycin	Clavacin
<i>B. subtilis</i>	19,000,000 †	60,000,000	2,000,000	
<i>S. aureus</i>	9,500,000 †	20,000,000	2,000,000	200,000
<i>S. lutea</i>	38,000,000 †	60,000,000	4,000,000	100,000
<i>Cl. welchii</i>	1,500,000 †	1,000,000	125,000 §	500,000
<i>B. anthracis</i>	1,000,000 †	2,500,000	
<i>Pr. vulgaris</i>	4,000 †	500,000	
<i>Br. abortus</i>	2,000 †	10,000	500,000	
<i>E. coli</i>	<1,000	5,000	1,000,000	100,000
<i>S. schottmülleri</i>	<1,000	<10,000	500,000	60,000
<i>M. tuberculosis</i>	<1,000	7,000,000	
<i>K. pneumoniae</i>	<1,000	1,000,000	
<i>S. marcescens</i>	<1,000	<5,000	1,000,000	60,000

* Considerable variation is found among different strains of the same organisms. Two crude preparations of penicillin used in these tests designated either by † or by ‡.

§ *Cl. butyricum* used.

distinct physical, chemical and biological properties which make them ideal potential chemotherapeutic agents. These can be described briefly as follows:

1. Antibiotics are highly selective in their action upon different micro-organisms. This selectivity extends not only to genera and species but even to strains and individual cells. Some antibiotics attack mainly gram-positive bacteria and only to a limited extent the gram-negative forms; others affect alike various types of bacteria within each of these two groups. Some have no effect

No antibiotics that are active against the smaller viruses have so far been isolated although the indications are that such exist. The variations in the action of antibiotics upon different bacteria and other micro-organisms are both qualitative and quantitative in nature. This suggested the concept of an "antibiotic spectrum," which records the selective action of a given antibiotic upon a number of representative bacteria and other micro-organisms. This is illustrated in Tables I and II.

2. The antibiotics represent a large num-

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ber of chemical compounds, ranging from simple substances containing only C, H and O, to more complex forms which contain nitrogen, sulfur and even chlorine, as shown in Table III. They vary greatly in chemical structure as shown in the accompanying

from one another in the presence or absence of certain chemical groups. This may affect their quantitative activity upon different bacteria. This is true, for example, of the penicillins or the streptomycins. The various compounds within each antibiotic complex

TABLE II
TYPICAL ANTIBIOTIC SPECTRA OF SEVERAL ANTIBIOTICS PRODUCED BY DIFFERENT MICRO-ORGANISMS³—
MINIMUM INHIBITORY CONCENTRATION OF ANTIBACTERIAL SUBSTANCES IN MICROGRAMS PER ML.

Antibacterial Substance	B. mycoides	B. subtilis	S. aureus	E. coli	K. pneumoniae	P. aeruginosa	M. phlei
Aspergillilic acid.....	2	4	4	62	13	1,000	125
Biformin.....	13	0.04	0.3	1.7	1.7	53	0.6
Citrinin.....	32	16	16	>1,000	125
Dihydrostreptomycin.....	0.25	0.5	0.03	0.25	0.13	4	0.25
Gliotoxin.....	0.25	0.25	0.15	25	6	500	4
Helvolic acid (fumigacin).....	4	16	1	>1,000	4	>32
Kojic acid.....	2,500	620	1,250	2,500	620	5,000	2,500
Mycophenolic acid.....	500	250	250	500	>1,000	>1,000	500
Patulin (clavacin).....	16	4	8	8	8	125	16
Penicillilic acid.....	32	8	16	64	64	1,000	64
Penicillin G.....	30	0.03	0.016	14	110	500	14
Penicillin X.....	30	0.06	0.03	14	240	500	29
Pleurotin.....	3	0.2	0.8	>500	>500	>32
Spinulosin.....	125	125	63	250	250	500	250
Streptomycin.....	0.13	0.25	0.03	0.25	0.13	4	0.25
Streptothricin.....	100	0.8	0.1	0.3	0.1	2	7

structural formulas. Some of the antibiotics comprise several compounds which differ

TABLE III
CHEMICAL COMPOSITION OF CERTAIN ANTIBIOTIC SUBSTANCES

- I. Compounds containing C, H and O:
 - Kojic acid $C_6H_6O_4$
 - Clavacin $C_7H_6O_4$
 - Penicillilic acid $C_8H_{10}O_4$
 - Pyolipic acid $C_{10}H_{20}O_3$
 - Gladiolic acid $C_{11}H_{10}O_6$
 - Mycophenolic acid $C_{17}H_{20}O_6$
 - Viridin $C_{20}H_{16}O_6$
 - Fumigacin, helvolic acid $C_{32}H_{44}O_8$
- II. Compounds containing C, H, O and N:
 - Hemipyocyanin $C_{12}H_8ON_2$
 - Aspergillilic acid $C_{12}H_{20}O_2N_2$
 - Pyocyanin $C_{13}H_{10}ON_2$
 - Streptomycin $C_{21}H_{37-39}O_{12}N_7$
 - Pyo II $C_{34}H_{46}O_4N_2$
 - Actinomycin $C_{41}H_{56}O_{11}N_8$
 - Polypeptides—Gramicidin, tyrocidine, etc.
- III. Compounds containing C, H, O, N and S:
 - Penicillin $C_9H_{11}O_4SN_2R$
 - Gliotoxin $C_{13}H_{14}O_4S_2N_2$
- IV. Compounds containing chlorine:
 - Ustin $C_{19}H_{15}O_8Cl_3$
 - Chloromycetin
 - Aureomycin

are produced by different strains of a given organism, by different organisms or by the same organism under different conditions of culture.

3. Certain micro-organisms are capable of producing more than one antibiotic. The ability of *Pseudomonas aeruginosa* to form pyocyanase, pyocyanin and hemipyocyanin has long been known; to these have recently been added the pyo-compounds, pyolipic acid and certain others. *Bacillus subtilis* forms a number of polypeptides which possess antibiotic properties; it is sufficient to mention bacitracin, subtilin and bacillin. *Aspergillus flavus* produces aspergillilic acid and certain forms of penicillin. *A. fumigatus* yields at least four antibiotics, namely, spinulosin, fumigatin, fumigacin and gliotoxin and possibly others. *Streptomyces griseus* forms the antibacterial agents streptomycin and mannosidostreptomycin, the antifungal agent actidione and the antitrichomonas agent streptocin; other strains of *S. griseus*

produce grisein and other antibiotics. Various strains of *S. lavendulae* are able to yield streptothricin, lavendulin, streptin, streptolin and others. The culture filtrates of some of the antibiotic-producing organisms are also active against various bacterial toxins whereas the purified antibiotics do not possess that activity; this phenomenon has been designated as the *antidotic effect*.

4. Some antibiotics are produced by several different organisms. The various penicillins are formed by *P. notatum*, *P. chrysogenum*, *A. flavus*, *A. giganteus*, *P. crustaceum* and a number of other fungi. The same is true of gliotoxin, clavacin and various other antibiotics. Clavacin is known under a number of different names, depending on the organism from which it was isolated. This accounts for "claviformin," "patulin," "clavatin," "expansin" and "leucopin." Actinomycin is produced by a large number of different actinomycetes belonging to the genus *Streptomyces*. Streptomycin has been isolated from cultures of *S. griseus* and *S. bikiniensis* and from cultures of organisms that are also able to form other antibiotics, such as streptothricin.

5. The nature of the substrate in which the antibiotic exerts its antibacterial effect may influence the nature and extent of this effect. Certain constituents of the medium reduce the activity of an antibiotic by neutralizing its action or by adsorbing or by inactivating the antibiotic. This is particularly true of the effects of salts and serum proteins, which may thus explain the differences in the *in vitro* vs. *in vivo* activities of certain antibiotics.

6. Some antibiotics, such as penicillin, are readily destroyed by various micro-organisms whereas others, such as streptomycin, are highly resistant to microbial action.

7. The mode of action of antibiotics upon bacteria varies. Some interfere with the growth of bacteria and with their cell division; some influence microbial respiration; others affect the utilization of essential metabolites by the bacteria.

8. Antibiotics vary greatly in their toxicity to animals. Some, like actinomycin and

xanthomycin, are extremely toxic; others, like penicillin, have virtually no toxicity at all; most of the other antibiotics fall between these two extremes. The specific effect of an antibiotic upon the various animal tissues also varies greatly.

9. Some antibiotics can be modified chemically so as to reduce their toxic properties. This is true of dihydrostreptomycin which is a reduced form of streptomycin.

10. Bacteria sensitive to a given antibiotic may gradually develop resistance to it when allowed to be in contact with it for some time. Different antibiotics vary greatly in this respect. Some, like streptomycin, allow rapid development of resistance of most bacteria originally sensitive to it; others, like penicillin, allow only gradual development of resistance of very few sensitive bacteria. The process of re-acquirement of sensitivity or loss of resistance also differs with the antibiotic and with the bacteria. A given bacterial culture may contain one or more cells far more resistant to a certain concentration of an antibiotic than the great majority of the cells in that culture; when these resistant cells develop, they give rise to a culture which shows far greater resistance to the particular antibiotic than the original culture.

Because of these differences in chemical properties, antibacterial activities and effect upon body tissues, antibiotics vary greatly in their chemotherapeutic potentialities. This is largely the reason why of more than one hundred antibiotics that have already been isolated and described, only five or six have so far found practical application in the treatment of infectious diseases.

HISTORICAL BACKGROUND

In tracing the historical development of our concepts of the nature and utilization of antibiotics, three distinct periods must be recognized: (1) The early observations of the growth of micro-organisms in mixed cultures, the effects of one organism upon another when grown in artificial media and the interactions among various organ-

isms found in a natural environment including mixed infections. (2) The first attempts to isolate, from pure cultures of bacteria and other micro-organisms, crude preparations or purified chemical substances which possessed antibacterial properties; these attempts were often accompanied by efforts to utilize the isolates for the control of infectious diseases. (3) The last decade when antibiotics became recognized as important chemotherapeutic agents and their role in the treatment of numerous diseases became permanently established.

To illustrate further these distinct phases in the history of a new branch of science, that of the science of antibiotics, a few additional facts may be cited:

Early Observations. From the early days of bacteriology it was recognized that various micro-organisms are capable of repressing, in culture, the growth of other organisms. Mixed infections were found to behave differently from the same type of infections caused by single disease-producing agents; in such mixed infections some of the organisms were able to repress the growth of others. An attempt was made to utilize such organisms, as in the treatment of infections by less pathogenic organisms, such as anthrax with streptococci or with *Ps. aeruginosa*.

Early students of the microbiologic population of the soil observed that the great majority of disease-producing organisms which find their way into the soil gradually tend to disappear there. This was shown to be due largely to the presence in the soil of microbes, known as antagonists, which brought about destruction of the disease-producing forms.

Those sporadic attempts that were made to utilize for chemotherapeutic purposes either the saprophytic organisms themselves or the chemical substances that they produced in culture media failed completely or at best yielded rather inconclusive results. This was due, partly at least, to an insufficient differentiation between the activities of the living organisms and of their

chemical products which possessed antibacterial properties.

The evidence submitted in support of these isolated observations did not exert any profound influence upon the understanding of the mechanism of disease or upon the course of medical practice. Although many of these studies were fundamental in nature, the results obtained did not fit into a well coordinated pattern. They certainly did not point to the great potentialities in the field of utilization of antibiotics for disease control as it is visualized today. Without reviewing in detail the numerous observations in this field, a few illustrations will suffice:

In 1885 Cantani attempted to utilize certain common bacteria for the treatment of tuberculosis. Cultures of the saprophyte of doubtful purity were blown into the lungs of the patients. A certain improvement in their condition resulted; this was accompanied by the appearance of the saprophytic organism in the sputum. Emmerich demonstrated somewhat later that an injection of streptococci into animals enabled them to withstand infection from *B. anthracis*. Bouchard also showed that inoculation of animals with *Ps. aeruginosa* gave protection against anthrax.

The replacement of pathogenic bacteria in a given infection by saprophytic organisms or by potentially lesser pathogens forms a most interesting chapter in the history of microbiology and medical practice. Introduction into the human intestines of harmless lactic acid organisms to replace potentially dangerous enteric bacteria was initiated by Metchnikov and later found wide application. The use of *Escherichia coli* for the purpose of replacing pathogenic bacteria in the gut was first postulated by Nissle in 1916; this was the vogue for awhile. In the treatment of diphtheria recourse was had to use of several bacteria, ranging from lactic acid organisms to *Staphylococcus aureus*; the resulting effects were not always too favorable to the host, as one might expect from an excessive application of *S. aureus*. Use of various forms of yeasts, by different

methods of administration, also had a certain popularity at one time, again with rather uncertain results. Cultures of lactobacilli were used not only for internal but also for external administration, as in the treatment of vaginal trichomoniasis. Application of cultures of *Lactobacillus acidophilus* was said to be beneficial in the treatment of various forms of diarrhea and dysentery.

The first attempt to use an antibiotic preparation must be credited to Emmerich and Löw who, in 1899, utilized pyocyanase for combating infections. This was followed by numerous other efforts of a similar nature. The results obtained were rather uncertain and often disappointing in spite of the fact that at times some favorable indications were obtained. Pyocyanase preparations appeared to find special application in surface therapy; they were used clinically in a number of infections, including nasal sinuses, Vincent's angina, diphtheria and, in veterinary practice, streptococcal mastitis.

Fungus products as well were tried for their clinical potentialities. In 1913, Vaudremer, for example, used the metabolic products of *A. fumigatus* for combating tuberculosis; although some 200 patients were thus treated, the results were again rather inconclusive. Gratia utilized cultures of certain actinomycetes for the purpose of lysing typhoid bacteria; the preparations thus obtained were designated as *mycolysates* and were used for immunizing purposes.

A number of other microbiologic preparations were tested for their therapeutic power. Frequently the total culture filtrate of the organisms was used. These preparations were occasionally found to possess marked antibacterial properties. Some of them were active against bacteria not only in the test tube but also in experimental animals. A few of them were even used clinically, with varying degrees of success, in the treatment of various human infections, such as anthrax, diphtheria and tuberculosis. The results obtained from these investigations were not sufficient, however,

to warrant drawing broad conclusions concerning the possibility of utilizing the metabolic products of micro-organisms as chemotherapeutic agents, except under varied special conditions and upon a limited number of infections.

First Isolation of Antibiotics. Among the three major groups of micro-organisms largely responsible for the production of antibiotics at the present time, namely, the bacteria, fungi and actinomycetes, the first received the earliest consideration. The ability of certain bacteria belonging to the pyocyanus group to inhibit the growth of and even to kill other bacteria was investigated nearly six decades ago. This organism yielded a preparation designated as *pyocyanase*, which may be considered as the first antibiotic ever isolated and described. This ability of certain bacteria to yield substances that possessed antibacterial properties was considered to be a freak and was not visualized as having a widespread distribution among micro-organisms. Pyocyanase was actually believed to be an enzyme system that had the capacity of bringing about lysis of certain bacterial cells.

A mere review of the voluminous literature on the compounds possessing antibacterial properties which have been isolated from the culture medium and from the cells of *Ps. aeruginosa* would take far more space than would be justified in this brief summary of the field of antibiotics. Suffice to say that even at the present time, after more than half a century of research, this organism and its characteristic capacity of causing inhibition of bacterial growth still continue to attract the attention of many investigators. Attention is directed only to the recent work of Doisy and his associates on the pyo-compounds and of Bergström, Theorell and Davide on pyolipic acid. Although numerous claims have been made concerning the practical application of some of the preparations obtained from this organism, none of these preparations has so far become established as a recognized chemotherapeutic agent.

The isolation of antibiotics from spore-forming bacteria also covers extensive literature. It is sufficient to draw attention to the earlier work of Nicolle, Pringsheim and Much, on specific organisms belonging to the *B. subtilis*, *B. mesentericus* and *B. mycoides* groups, and to numerous other investigations on the ability of various other spore-forming bacteria to inhibit the growth of bacteria and other micro-organisms, including many human and animal pathogens. These studies culminated in 1939 in the work of Dubos, who isolated from cultures of the *B. brevis* group a series of polypeptides which possessed remarkable antibacterial properties. The *tyrothricin* complex contained two crystalline compounds, *gramicidin* and *tyrocidine*. This was followed by a survey of numerous other products of spore-forming bacteria, some of which appear to possess remarkable properties of promising chemotherapeutic agents.

The ability of fungi to inhibit the growth of other micro-organisms was also recognized before the end of the last century. Gosio is credited with having isolated from a culture of *Penicillium* an antibiotic substance designated as *mycophenolic acid*. These early studies were followed by the work of Duchesne and Vaudremer, to be culminated in the work of Fleming in 1929, who isolated from a culture of *Penicillium notatum* a preparation designated as *penicillin* which possessed remarkable antibacterial properties. More than a decade elapsed, however, before Florey, Chain and their associates demonstrated, in 1940 to 1941, its remarkable chemotherapeutic properties. This was soon followed by a deluge of investigations on the production of penicillin, as well as on the general subject of the production of antibiotic substances by fungi. One other antibiotic isolated during the early period must be mentioned here, namely, gliotoxin. Although this agent was crystallized and its antifungal properties were established, its antibacterial activities were not recognized. Certain other products of fungus metabolism were isolated by Raistrick and his collaborators, but the antibacterial poten-

tialities of these products were not established until later.

Although various observations have been made in the past concerning the ability of certain actinomycetes to inhibit the growth of bacteria, the comprehensive study of the formation of antibiotics by this group of organisms dates only to the last decade. The two outstanding groups of investigations previous to 1939 are: first, those of Gratia and Welsch on the production of a lytic system by an organism designated first as *streptothrix* and later as *Actinomyces albus*, the active agent finally being named *actinomycin* and, second, the surveys of several Russian investigators on the occurrence of antagonistic actinomycetes in the soil and their selective action upon various bacteria. The systematic investigation of the production of antibiotics by actinomycetes, begun in 1940 by the workers of the Department of Microbiology of the New Jersey Agricultural Experiment Station and which resulted in the isolation of actinomycin, micromonosporin, streptothricin, streptomycin, grisein, streptocin and neomycin, gave a marked stimulus to the study of these organisms, with the result that more than thirty compounds have now been isolated. These vary greatly in their chemical nature, antimicrobial spectra, toxicity to animals and chemotherapeutic potentialities.

The production of antibiotic substances may thus be considered as a phenomenon widely distributed among micro-organisms. The nature of the antibiotic and its quantitative yield depend upon the organism, the manner of its nutrition and conditions of growth. One type of antibiotic may be produced by a certain organism grown in surface culture and another type under submerged conditions. *A. flavus*, for example, produces largely aspergillic acid in stationary culture and flavicin, a penicillin-like substance, produces the acid in submerged culture. The nutrition of *B. brevis* and the production of tyrothricin by this organism are quite different under submerged conditions of growth as compared to stationary cultures. Certain organisms require specific

nutritional or growth-promoting agents or precursors for the formation of a given substance; other antibiotics are produced in synthetic or simple organic media.

Attempts have been made to explain the capacity of antagonistic micro-organisms to produce antibiotics on the basis of their struggle for existence in nature. The available evidence does not fully justify this assumption. Although the presence in the soil of certain toxic compounds, which may be classified with the antibiotics, has been demonstrated, no evidence has as yet been submitted to prove that the accumulation or even the formation by micro-organisms of antibiotics under soil conditions is based upon competition for either nutrients or space.

The available evidence leads to the conclusion that various micro-organisms have the inherent capacity of inhibiting the growth of or killing other organisms. This is usually brought about by the formation of specific chemical agents, namely, antibiotics. Such properties may or may not be stimulated by the addition to the substrate of sensitive organisms. The ability to produce antibiotics may be due to strain selectivity of the organism, to improvement in the culture medium for its development or to stimulation of a latent capacity which it possesses.

The Last Decade. To bring all these cursory observations together into one system and thus lay the groundwork for the science of antibiotics, and especially to determine their potentialities as chemotherapeutic agents, a synthesis was needed. This required the coordinated efforts of the microbiologist, chemist, pharmacologist and clinician in order to test various cultures of micro-organisms obtained from different substrates for their ability to inhibit bacterial growth and produce antibiotic substances, to isolate such substances from the metabolite solution, to evaluate their toxicity and effectiveness in the animal body and finally to test them clinically. This synthesis was brought about in 1939 to 1940, when isolation of tyrothricin, soon followed

by the re-isolation of penicillin, established beyond doubt that substances of microbial origin, the antibiotics, can find an important place in chemotherapy, not only of human diseases but also of animal and possibly even of plant diseases.

It is of special interest to draw attention to the fact that three groups of investigations, which have thus laid the foundation for the recent advances in our knowledge of antibiotics, dealt with the three groups of micro-organisms that are now considered to be the most important producers of antibiotic substances. (1) Investigation of the tyrothricin complex produced by *B. brevis*. This not only served to focus attention upon an important group of antibiotics, the bacterial polypeptides, but also laid the foundation for extensive studies of aerobic spore-forming bacteria. This led to the isolation of a large number of compounds, designated as *gramicidin S*, *subtilin*, *bacitracin*, *licheniformin*, *polymyxin*, *aerosporin*, *bacillin*, *eumycin*, *subtilysin*, *endosubtilysin* and others. (2) The work on the penicillin complex. This was followed by numerous studies on the production of antibiotics by fungi, with major emphasis on the various forms of penicillin. These studies resulted in isolation of a large number of antibiotics, including *aspergillin*, *aspergillic acid*, *citrinin*, *clavacin* (*claviformin*, *patulin*), *fumigacin* (*gladiolic acid*), *glutinosin*, *javanicin*, *mycocidin* and penicillin-like substances. With the exception of penicillin, none of the fungus antibiotics has so far shown any outstanding promise as a chemotherapeutic agent. (3) Investigation of the production of antibiotics by actinomycetes. This resulted first in the isolation in 1940 of actinomycin—a highly toxic compound. Others followed, most important of which are, in order of isolation, *streptothricin*, *streptomycin*, *chloromycetin*, *aureomycin* and *neomycin*, several of which proved to be highly important chemotherapeutic agents. A large number of other antibiotics have been isolated from cultures belonging to this group, such as *micromonosporin*, *nocardin* and *proactinomycin*.

WHAT ANTIBIOTICS ARE DESIRABLE?

It is now generally recognized that for a new antibiotic to qualify as a chemotherapeutic agent it must satisfy certain definite requirements, the most important of which may be summarized briefly as follows: (1) It must be selective in its action against various groups of micro-organisms and should not be a generalized protoplasmic poison. (2) It must have desirable antibacterial properties, that is, it must affect bacteria or other micro-organisms that are not subject to the action of other antibiotics or synthetic chemical compounds, or it must be more potent or more effective than others which it is to replace. (3) It must be active in the presence of body fluids. (4) It must not be destroyed by tissue enzymes. (5) It must not be toxic, or at least not too toxic to animals as a whole, or to individual cells, such as leukocytes, or to tissues, such as kidneys. (6) Preferably it should possess desirable physical and chemical properties, such as solubility in water and a certain degree of stability. (7) It should be excreted readily, but not too rapidly, from the animal system and should not accumulate there and produce undesirable after-effects.

Some of the more interesting antibiotics, even if not always the most desirable, may now be discussed in somewhat greater detail.

ANTIBIOTICS OF BACTERIA

Large numbers of bacteria, including gram-positive and gram-negative forms, spore-forming and non-spore-forming cocci and bacilli, have the capacity of producing antibiotics. Some of these substances are active largely upon gram-positive bacteria; some are active also upon gram-negative forms; some are able to attack fungi. A few of them have found application as chemotherapeutic agents. Only some of these need be considered in further detail.

Tyrothricin is made up of about 20 to 25 per cent gramicidin and 60 per cent tyrocidine. The first is a large polypeptide, having a molecular weight of about 2,826, with a high content of tryptophane and cer-

tain natural and unnatural isomers of other amino acids. It is insoluble in water and is active only against gram-positive bacteria both *in vitro* and *in vivo*. Tyrocidine has a molecular weight of 2,564 and is composed of *l*-amino acid residues and 3 residues of *d*-phenyl alanine. It is active against various bacteria only *in vitro*. It is inhibited by serum proteins.

Polymyxin is a basic substance soluble in water. It is highly active against various gram-negative bacteria, both *in vitro* and *in vivo*; its activity is not affected by the reaction of medium within a range of pH 5 to 8. It appears to be identical with a similar antibiotic described as *aerosporin*.

Bacitracin is produced by a member of the *B. subtilis* group. It is a neutral compound, soluble in water and in organic solvents. Its polypeptide nature has recently been questioned. It is highly active against certain gram-positive bacteria, has limited toxicity in animals and clinically exerts a marked effect in the treatment of infections caused by sensitive bacteria.

Subtilin is produced by a strain of *B. subtilis*. It is insoluble in 95 per cent alcohol but is soluble in 70 per cent. It is active only against gram-positive bacteria, including *M. tuberculosis*, both *in vitro* and *in vivo*. It is also active against a number of pathogenic fungi, *Endamoeba histolytica* and *Trypanosoma equiperdum*. Its low toxicity and *in vivo* activity make it a potential chemotherapeutic agent.

Licheniformin was isolated from *B. licheniformis*, a strain of *B. subtilis*. It is not active against gram-negative bacteria but is effective against certain gram-positive forms, including *M. tuberculosis*.

Nisin is produced by certain lactic acid streptococci. It is active, both *in vitro* and *in vivo*, against various gram-positive bacteria, including *M. tuberculosis*. It is similar in many respects to *diplococcin*, another antibiotic produced by lactic acid cocci, a protein-like material of small molecular weight.

Colicins are a group of antibiotics produced by certain strains of *Escherichia coli*

and other enteric bacteria. They are highly specific in their action upon other enteric bacteria, species of *Shigella* being most sensitive. The various colicins differ in their antibiotic spectra and in their physiochemical properties. Some cultures produce several colicins with different antibiotic spectra. They are peptides in nature and are destroyed by proteolytic enzymes; they are soluble in water, insoluble in organic solvents and heat-stable. Their potential chemotherapeutic value is questionable.

Pyo-compounds are extracted from the cells of *Ps. aeruginosa* with hot alcohol. They are nitrogenous compounds ($C_{34}H_{46}N_2O_4$ etc.) and are active against gram-positive bacteria, apparently *in vitro* only.

Pyolipic acid has also been obtained from *Ps. aeruginosa*. It has the composition of $C_{11}H_{22}O_3$ and is active against *M. tuberculosis*.

Numerous other bacteria were found to have the capacity of producing antibiotic substances but most of them, as in the case of marine bacteria, have been but little studied.

ANTIBIOTICS OF FUNGI

Fungi form by far the largest group of organisms which have the capacity to produce antibiotics. Some of the earliest and some of the most recent compounds have been isolated from this group of microorganisms. Very few of the *Phycomycetes* yielded any antibiotics. Only one preparation active against *Tr. equiperdum* was reported. It is soluble in organic solvents and in water. The *Basidiomycetes* have yielded a number of compounds, some of which, notably *polyporin* and *clitocibin*, were believed to offer potentialities as chemotherapeutic agents, the latter against *M. tuberculosis*. Certain agarics were also found to have a marked effect upon this organism. The pigment lactaroviolin is active in very low concentrations. Some of the antibiotics isolated from lichens, such as *usnic acid* and *ramularin*, have also been found to be highly effective against the tubercle organism not only *in vitro* but also *in vivo*.

The largest number of antibiotics have

been isolated from *Hyphomycetes*. Some of these are toxic and offer, therefore, little promise of becoming chemotherapeutic agents; the potentialities of others have still been little investigated. Among the more important antibiotics the *penicillins* occupy the leading place. Although the greatest interest is manifested in the clinical application of penicillins, considerable knowledge has been gained of the physiology of *P. notatum* and *P. chrysogenum* and the biochemical problems concerned in penicillin production and the mode of action of penicillin upon bacteria. Various species of *Aspergillus* have also been found to produce penicillin. In addition some form other antibiotics, such as *aspergillic acid*.

Only a few of the antibiotics produced by fungi are described in detail herein.

Penicillin. At least six closely related compounds comprise the penicillin group. They are produced by a number of fungi, chiefly members of the *P. notatum-chrysogenum* groups. They are active largely against gram-positive bacteria and have little activity against gram-negative rods and acid-fast bacteria, fungi or viruses. The penicillins are relatively non-toxic and have found extensive application in chemotherapy, notably in diseases caused by cocci (staphylococci, gonococci, meningococci), gram-positive rod-shaped bacteria, including both aerobic and anaerobic forms, and spirochaetes.

Clavacin. Clavacin is active against various gram-positive and gram-negative bacteria, acid-fast bacteria and fungi. It is very toxic to both animals and plants and therefore has not found any practical application.

Fumigacin (helvolic acid). Fumigacin is produced by various strains of *Aspergillus fumigatus*, an organism capable of producing a variety of other antibiotics, notably *gliotoxin*, *fumigatin*, *spinulosin* and an anti-tumor factor. It is soluble in organic solvents and insoluble in water. It mainly inhibits gram-positive bacteria. It is fairly toxic and has found no application in chemotherapy.

Gliotoxin. Gliotoxin is produced by a number of fungi. It is soluble in organic

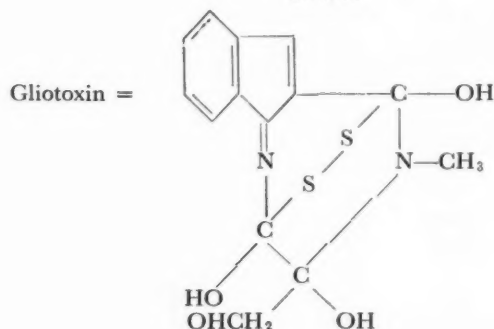
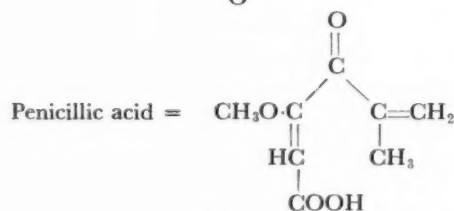
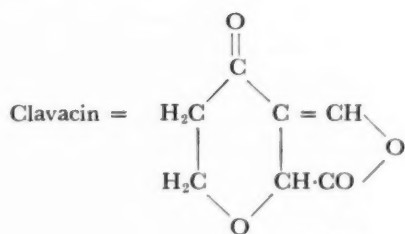
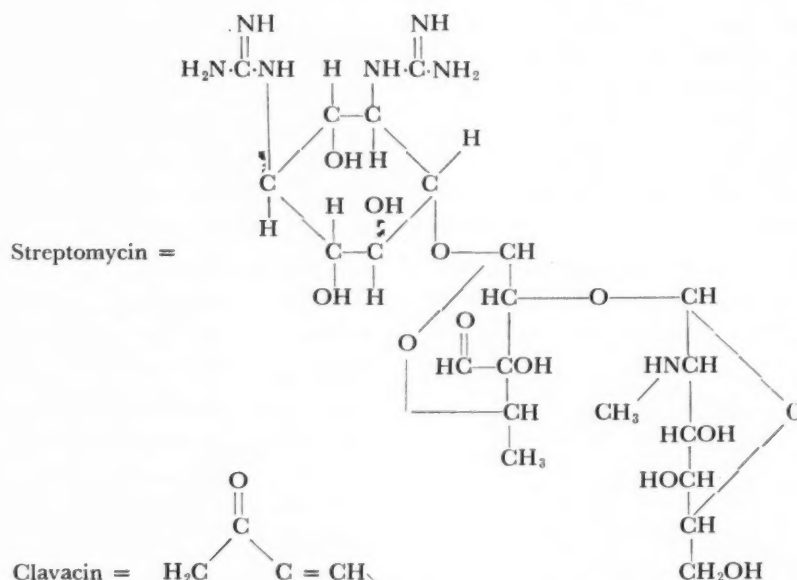
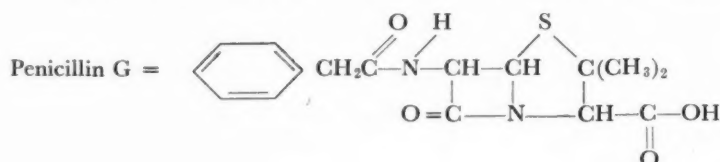
solvents and insoluble in water; it is active against a large number of bacteria and fungi. It is highly toxic.

Chetomin. Chetomin is produced by *Chaetomium cochliodes*, largely in its mycelium. It is soluble in a number of organic solvents but not in water or petroleum ether. It is

active only against certain gram-positive bacteria. It is not toxic but it is not active *in vivo*.

Penicillic acid. Penicillic acid is, like clavacin, a fairly simple compound. It is soluble in water and in organic solvents. It is produced by a variety of fungi. It is

CHEMICAL STRUCTURE OF SOME TYPICAL ANTIBIOTICS



active against a number of gram-positive and gram-negative bacteria.

Ustin. Ustin is a chlorine-containing antibiotic ($C_{19}H_{15}O_5Cl_3$). It is an acidic substance soluble in ether. It inhibits various gram-positive and acid-fast bacteria.

ANTIBIOTICS OF ACTINOMYCETES

Among the various groups of micro-organisms which are now being extensively investigated as potential producers of antibiotics, the actinomycetes occupy a prominent place. Many thousands of cultures, largely members of the genus *Streptomyces*, are being isolated and tested in numerous laboratories throughout the world. This is due to the ease with which these cultures can be obtained from soils, manures, peats, river mud, dust and other natural substrates; to the large proportion of cultures (10 to 50 per cent) that can be shown by simple methods of testing to possess antibacterial properties; and to the great practical potentialities of some of the antibiotics produced by these organisms, as shown to be the case for streptomycin.

Among the more promising antibiotics the following may be listed:

Streptomycin. Streptomycin is produced primarily by certain strains of *Streptomyces griseus*. It is isolated from the culture by adsorption on charcoal and removal with acid alcohol. It is soluble in water and insoluble in organic solvents. It is heat-stable and resistant to attack by micro-organisms. It is active against various gram-positive and gram-negative bacteria and against acid-fast bacteria, but not fungi. It is not very toxic and is used extensively in the treatment of numerous infections caused by gram-negative and penicillin-resistant gram-positive bacteria as well as upon tuberculosis. It allows ready development of resistance among sensitive bacteria.

Streptothricin. Streptothricin is produced by certain strains of *S. lavendulae*. It possesses similar properties to streptomycin but it is more toxic to animals. It is not active against various bacteria sensitive to strepto-

mycin (*B. mycoides*, *B. cereus*, *S. marcescens*) and it is active against fungi.

Chloromycetin. Chloromycetin contains organic chlorine in its molecule. It is produced by *S. venezuelae*. It is insoluble in water but soluble in organic solvents. It is active against various bacteria, against rickettsiae and against the larger viruses.

Aureomycin. Aureomycin is produced by *S. aureofaciens*. It is water-soluble, not very toxic, active against various gram-positive and gram-negative bacteria and rickettsiae; it can be administered by mouth. It is not very stable, especially in the presence of certain organic compounds.

Neomycin. Neomycin is produced by an organism closely related to *S. fradiae*. It is water-soluble and stable. It is active against various bacteria, including mycobacteria and streptomycin-resistant organisms. It is not active against fungi.

Actidione and Streptocin. These antibiotics, produced by various strains of *S. griseus*, are soluble in organic solvents. The first is primarily active against yeasts and fungi, the second is active against gram-positive bacteria and certain trichomonads.

PRODUCTION OF ANTIBIOTIC-LIKE SUBSTANCES BY PLANTS (PHYTONCIDES)

Various green plants were found to produce chemical compounds which have antibacterial properties similar to those of typical antibiotics. Some of these have been isolated and studied in detail. It is sufficient to mention allicin, a colorless oil, produced by *Allium sativum*; cassic acid produced by *Cassia reticulata*; crepin produced by *Crepis taraxacifolia*; pinosylvin produced by *Pinus sylvestris*; protoanemonin produced by *Anemone pulsatilla* and tomatin produced by the common tomato plant. They vary greatly in chemical composition; some are simple compounds, containing C, H and O; others also contain N or S. They vary in their activity upon micro-organisms and in their toxicity to animals. Certain lichens, such as spanish moss, also produce antibiotic-like materials, some of which, like usnic acid, are highly active upon the tubercle bacilli.

So far none of these plant products has found wide application in chemotherapy. It is of interest to mention the fact that quinine, a plant product, still represents an outstanding agent for the control of an important human infection, malaria.

PRODUCTION OF ANTIBIOTIC-LIKE SUBSTANCES BY ANIMALS

Animals also produce a number of substances which are characterized by antimicrobial properties similar to those of true antibiotics. One need only mention lysozyme, found in saliva, in eggs, in tears and in various mammalian tissues; erythrin, found in red blood cells; lactenin, present in milk and active upon lactic-acid bacteria; certain excreta of worms and certain protozoa.

Lysozyme, perhaps the best known of the animal products, is a polypeptide and brings about the lysis of a variety of bacteria, notably micrococci. It is water-soluble and is precipitated by various organic compounds.

None of these antibiotics have found practical application. Their role of protective mechanisms of animals against bacterial infections is still to be established.

ANTIBIOTICS AND DISEASE CONTROL

Only very few antibiotics have found practical application in the treatment of generalized or special bacterial infections or infections caused by other micro-organisms. The most important chemotherapeutic agents are the penicillins and streptomycin. Tyrothricin is used in the treatment of localized infections. Bacitracin, polymixin, aureomycin and chloromycetin appear to offer definite promise either as supplements or as independent chemotherapeutic agents. Penicillin, tyrothricin and bacitracin are active largely against gram-positive bacteria, whereas streptomycin, aureomycin and polymyxin are active against both gram-positive and gram-negative bacteria as well as against acid-fast bacteria. Aureomycin and chloromycetin are active against rickettsiae and some of the larger viruses. Strepto-

thricin is active against fungi. Penicillin is highly effective against spirochaetes. Although similar in certain respects, these antibiotics possess distinct and characteristic antimicrobial spectra; they differ in chemical composition, in their mode of action on disease-producing and other bacteria and in their effects upon the cells and tissues of the host.

On the basis of available clinical information, utilization of antibiotics in the treatment of various infectious diseases can be summarized as follows, the diseases being grouped in several distinct categories:

Diseases Caused by Gram-positive Bacteria and Certain Gram-negative Cocci. The organisms causing these diseases are among the most sensitive to various antibiotics. The penicillins have found extensive application in treatment of these diseases. Bacitracin has the capacity of attacking some of these infections in a highly efficient manner. The tyrothricin complex has found application in treating wound infections. Bacteria made resistant to penicillin or strains naturally resistant to this antibiotic may still be sensitive to some of the other antibiotics, notably, bacitracin and streptomycin.

Diseases Caused by Gram-negative Bacteria. These bacteria, for the most part, are resistant to penicillin and to bacitracin but they are sensitive to several other antibiotics. One of these, streptomycin, has already found extensive application in the treatment of diseases caused by these organisms. Polymixin and aureomycin are other promising agents. The possibility of utilizing the synergistic action of two antibiotics, or of an antibiotic such as streptomycin with a synthetic agent such as sulfadiazine, offers promise of meeting the danger of rapid development of resistance of some of the bacteria to streptomycin; this has been done successfully in the treatment of certain forms of brucellosis and in certain other infections.

Diseases Caused by Mycobacteria. Because of their peculiar characteristics, diseases caused by acid-fast bacteria have proved to be among the most resistant to chemo-

therapy. *M. tuberculosis*, despite its high sensitivity to many antibiotics *in vitro*, can be attacked in the body only in a manner which involves selective tissue penetration and selective interference with the metabolism of these bacteria. The discovery that streptomycin can be utilized in the treatment of tuberculosis has provided a great stimulus in the search for new antibiotics that possess similar properties. This has given hope that the control of this highly important group of diseases is finally within our reach. The fact that streptomycin is not alone in this respect is indicated by the latent potentialities of a number of other antibiotics, such as neomycin, aureomycin, streptothricin, subtilin, nisin, clitocybin and pyolipic acid. The possible development of strains of *M. tuberculosis* resistant to streptomycin suggested the supplementary use of a synergistic agent, such as promin or other sulfones and para-aminosalicylic acid.

Spirochaetal Diseases. Several antibiotics, notably penicillin, have a remarkable effect upon diseases caused by spirochaetes. Use of penicillin in treatment of these infections gradually appears to be superseding the methods of treatment current before the advent of antibiotic therapy.

Rickettsial Diseases. A number of antibiotics are highly effective upon rickettsiae. The discovery of chloromycetin and aureomycin promises the final solution of the successful treatment of these diseases. Although no agent has yet been discovered which can be used successfully against such important diseases as the common cold or similar viruses, some of the larger viruses, such as psittacosis, lymphogranuloma and virus pneumonia, are sensitive to several antibiotics.

Fungus Diseases. A number of antibiotics, namely, hemipyocyanin, gliotoxin, clavacin, streptothricin, actidione and antimycin, are known to possess marked fungistatic and fungicidal properties. Undoubtedly one or more of these will in time find application in the control of some of the diseases caused by fungi, including both animal and plant diseases

Other Diseases. There are a large number of other infections, such as those caused by foreign cells, namely, tumors, for which no effective antibiotic is known at present. Although certain bacteria, fungi (*A. fumigatus*) and protozoa are known to be capable of attacking tumors, no successful chemotherapeutic agents have so far been found among the antibiotics.

Protozoan Diseases. Various protozoa capable of causing human infections are also subject to attack by antibiotics, as in the action of streptocin upon trichomonads, the therapeutic significance of which is still to be established.

Antibiotics have also found extensive application in the treatment of various animal diseases and of certain plant diseases.

MODE OF ACTION OF ANTIBIOTICS AND DEVELOPMENT OF RESISTANCE

The antimicrobial action of antibiotics is said to be primarily growth-inhibiting in nature, by interfering with cell growth and cell multiplication; the cell is thus made unable to grow and divide and it gradually dies. Antibiotics also possess marked bactericidal properties. The nature of the antibiotic, age of the bacterial cell, composition of the medium in which the organism grows, environmental factors of growth, all influence the effect of a given antibiotic upon bacteria. Most of the theories proposed to explain the mechanism of bacteriostatic and bactericidal activities of antibiotics are largely speculative in nature, due to insufficient experimental evidence submitted for their substantiation. Among these theories the following deserve consideration:

1. Antibiotics interfere with some of the metabolic processes of the bacterial cell by substituting for one of its essential nutrients. Substances that are structurally related to the normal cell nutrients may thus exert a specific inhibitory effect. These substances are taken up by the cell and cause blocking of the natural processes of growth. They also may interfere with utilization of the intermediary metabolic products. Streptomycin has been found, for example, to have

the capacity of blocking the metabolism of certain amino acids by bacteria. When growing in the presence of high concentrations of penicillin, *S. aureus* was found to adopt a different form of amino acid metabolism.

2. Certain antibiotics interfere with various enzymatic systems, notably the respiratory mechanisms of the bacterial cell. These enzymes are concerned not only with oxygen uptake and production of acid by the cells but also with the synthesis of essential metabolites and co-enzymes. The phosphate uptake by bacteria, accompanying glucose oxidation, is an illustration of an enzyme mechanism that can be interfered with. The antibiotic may affect respiration only indirectly by competing with a metabolite for a certain enzyme system.

3. An antibiotic may prevent the synthesis of some essential metabolite by the bacterial cell. Interference with the production and utilization of an essential growth-factor required by the cell can serve as an illustration of such interference. The combination of an antibiotic with a sulfhydryl group which is essential for cell multiplication is another illustration.

4. An antibiotic may interfere with utilization of iron by the bacterial cell or with the functioning of an iron-containing enzyme system, as in the action of aspergillilic acid.

5. The antibiotic may act as a detergent and affect the surface tension of the bacterial cells.

6. Prolongation of the lag phase, reduction of the growth rate, lowering of the stationary population and hastening of the death of the bacteria have also been considered as mechanisms of antibacterial activities. The action of an antibiotic upon the bacterial cell may be a function of several factors, as just listed.

Development of resistance of a given culture to an antibiotic is due to variation in the sensitivity of the cells within the culture. The extent and speed with which such resistance develops depend largely upon the nature of the antibiotic and upon

the organisms concerned. In recent years increasing utilization of penicillin and streptomycin for the control of a variety of bacterial infections has focused particular attention upon this phenomenon. These two antibiotics differ not only in their respective antibacterial spectra but also in the ease with which bacteria develop resistance to them. Streptomycin allows such development of resistance at a much more rapid rate and by a much larger number of organisms than penicillin and it loses such resistance much more slowly.

The sensitivity of different strains of *M. tuberculosis* to streptomycin was found to range from 0.095 to 0.78 $\mu\text{g}/\text{ml}$. This natural variation in sensitivity of a given organism to a certain antibiotic is of great practical importance from a chemotherapeutic point of view since it influences the selection of the particular antibiotic for the treatment of a given infection and the concentration of the antibiotic to be used in clinical practice. In addition to the natural variation in sensitivity of bacteria, originally sensitive organisms may become gradually more resistant or "fast" to a given antibiotic when allowed to be in contact with it either in the test tube or in the body of the host.

Penicillin and streptomycin differ in the degree with which the bacteria made resistant to them become sensitive again. Fastness of staphylococci to penicillin is not a permanent characteristic; bacteria made resistant lose such resistance when grown in penicillin-free normal broth and become susceptible again to relatively low concentrations of penicillin. Naturally resistant strains remain resistant, however, for much longer periods. Bacteria made resistant to streptomycin, however, may retain such resistance for a long time.

Different antibiotics differ greatly in the degree of development of resistance. *S. aureus*, for example, developed marked resistance to penicillin and to streptomycin, intermediate resistance to pyocyanin and to gliotoxin and none to aspergillilic acid. When the organism was made resistant to

penicillin, its biochemical reactions were lost, the cells becoming pleomorphic and gram-negative. When the organism was made resistant to streptomycin, its characteristic biochemical reactions were also suppressed but there was no noticeable change in its morphology.

Various explanations have been suggested for the development of resistance. These may be summarized as follows: (1) Sensitive cells in a given bacterial population are killed thereby enabling the more resistant cells to grow selectively. (2) More resistant mutants are formed in a sensitive population of bacteria. (3) Acquisition of new enzyme systems or new metabolic activities permit the organism to survive in spite of the presence of the particular growth-inhibiting agent. Demerec reported that resistance of *S. aureus* to penicillin originates through a mutation mechanism and that the antibiotic acts as a selective agent to eliminate the non-resistant members of the bacterial population; the degree of resistance can be increased by selection, this increase being more rapid with each selection step.

In the development of resistance by bacteria to streptomycin, bacteria were found to produce two types of variants: One appears in small numbers in all concentrations of the antibiotic; it gives rise to cultures which grow both in streptomycin-free and in streptomycin-containing media, its virulence for animals being similar to that of the original strain. The second appears in greatest numbers in concentrations of strep-

tomycin between 100 and 400 $\mu\text{g}/\text{ml.}$; this type becomes dependent upon the presence of streptomycin in the medium; it does not grow in media containing less than 5 $\mu\text{g}/\text{ml.}$ streptomycin and it is non-virulent unless the animal receives streptomycin.

Various cultures of bacteria are thus found to produce both "resistant" and "dependent" variants. The critical concentrations of streptomycin above which the sensitive strains do not grow are about the same as those below which the dependent variants do not grow. These results tend to confirm the concept that antibacterial agents act as metabolite antagonists, streptomycin interfering with some essential metabolite or metabolic process of the sensitive strains and serving as a metabolite or growth factor for the dependent strain. This relation can be reversible for the dependent strains, but it is permanent in the case of the resistant strains.

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Combined Staff Clinics

The Adrenal Cortex

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University and The Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ROBERT F. LOEB: Today we are going to review briefly the functions of the adrenal cortex as represented by two disorders which occur in man. In one of these, Addison's disease, we deal with hypofunction; in the other, Cushing's syndrome, we observe certain manifestations of hyperfunction.

Before embarking on the subject of the clinic, however, I should like to say a few words concerning the role of the endocrine glands in general. The activities of these structures, as demonstrated either by extirpation or by exhibition of their active principles, are quite extraordinary but it should not be forgotten that they play a role secondary to the intrinsic functions of the body cells. Life may go on in the absence of any one of the endocrine structures. Thus, total hypophysectomy is compatible with existence. Removal of the parathyroids does not lead to death, provided a source of calcium is made available. Total ablation of the thyroid does not result in death. Total destruction of the islands of Langerhans is compatible with existence; and indeed if accompanied by hypophysectomy or adrenalectomy, the diabetes is ameliorated. Total removal of the adrenal glands is compatible with existence if a proper external environment is provided for the tissues by maintenance of an adequate circulation through the administration of salt and water. Castration, of course, is compatible with maintenance of life. In other words, the organism as a whole can carry on the functions of oxidation, growth and cell division without any endocrine system. Perhaps it is best to consider the

endocrine glands as structures which are extraordinarily useful in meeting the exigencies of a complex society of cells; their function primarily is not to initiate the fundamental processes of metabolism but to expedite them, particularly under conditions of stress.

We might now turn directly to the subject of the discussion. I am going to outline for you some of the milestones in the history of the development of our knowledge in this field. The first observation of importance concerning the adrenal glands was made by Thomas Addison in 1849, and in 1855 he published his memorable monograph on "The Constitutional and Local Effects of Diseases of the Suprarenal Capsules" in which he pointed out that total destruction of these structures leads to death. The next year Brown-Séquard established the fact that bilateral ablation of the adrenal glands in animals resulted in death in the course of a few days. Perhaps the next important step was Abel's isolation of epinephrine from the adrenal medulla. It soon turned out that after ablation of the adrenal glands epinephrine *per se* would not maintain life; therefore, the essential vital functions apparently lay within the cells of the cortex. In 1909 Porges demonstrated the development of hypoglycemia in animals as well as in man following either extirpation or destruction of the adrenal glands. In 1916 E. K. Marshall first suggested that there might be a relation between the adrenal cortex and the kidney, because he observed that nitrogen retention and decrease in urine excretion followed bilateral adrenalectomy. Of course, this

was not evidence of a direct relationship but merely indicated the presence of severe shock with associated disturbances in renal function.

Around 1930 three groups of investigators prepared the first extracts of the adrenal

tients with Addisonian crises. It was shown also that this fall in serum sodium, as well as the abnormal elevation of serum potassium and urea nitrogen, could be alleviated by administration of sodium chloride and restoration of the serum

TABLE 1

SOME CLINICAL AND LABORATORY CHARACTERISTICS OF ADRENAL CORTICAL ACTIVITY

Hypoadrenalism	Hyperadrenalism (Cushing's Syndrome)
<i>Electrolyte and water metabolism</i>	
Weakness, nausea, vomiting, hypotension, dehydration, reduced blood volume, shock and death; sodium loss accompanied by chloride or bicarbonate loss, potassium retention, nitrogen retention, decreased ammonia excretion	Frequent high sodium and low potassium Hypertension
<i>Carbohydrate and protein metabolism</i>	
Weakness, C.N.S. symptoms, hypoglycemia, increased susceptibility to stress (alarm reaction); insulin sensitivity; ? decreased glyconeogenesis; ? increased carbohydrate utilization; decrease in urinary corticoids and 17-ketosteroids	Diabetes mellitus, insulin resistance, skeletal demineralization, capillary fragility, "plethoric appearance," changes in body form and skin, weakness; increase in urinary corticoids, occasional increase in 17-ketosteroids
<i>Pigmentation</i>	
? Electrolyte relationship	
<i>Sex function</i>	
Not significantly disturbed	Amenorrhea
<i>Immunity</i>	
Lymphoid hyperplasia Relation to protein metabolism	Depression of eosinophiles Lymphoid hypoplasia
<i>Nervous system instability</i>	
Mecholyl sensitivity and vagal death	Emotional instability

cortex which had some measure of physiologic activity. These groups were headed by Swingle and Pfiffner, Rogoff and Hartman. The next important advance was in isolation of the active adrenal cortical steroids and, as you know, there have been three outstanding contributors to this field, Reichstein in Switzerland and E. C. Kendall and Wintersteiner in this country. After these studies had been made progress became more rapid and the significant advances in our knowledge have become too numerous recently for detailed discussion at this time.

It was first demonstrated in this hospital in 1932 that there is a decrease in sodium concentration in the blood plasma in pa-

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sodium concentration. The clinical manifestations of weakness, nausea, vomiting, arterial hypotension and collapse could be initiated by withdrawal of salt from the diet and could be dispelled by the administration of salt and water even without cortical extract. Finally, it was shown that the water and electrolyte changes, at least in part, resulted from an increased loss of sodium and water with retention of potassium by the kidney. Accumulating evidence supports this view that the electrolyte disturbances result primarily from a loss of control of renal tubular epithelium normally exerted by the adrenal cortex.

The importance of loss of salt is demonstrable by the fact that, as indicated before,

life will go on for long periods of time in the absence of the adrenal glands in the dog, rat, indeed in man when adequate salt and water are provided. Harrop and also Allers kept totally adrenalectomized dogs alive six months by forced feeding of sodium chloride and the administration of water.

Loss of sodium from the body is accompanied by a loss of chloride or bicarbonate, or both. Also, as sodium, chloride and bicarbonate are lost from the blood and interstitial fluid, and in the absence of a corresponding loss of potassium, Muntwyler and also Darrow showed that there is a shift of water to the cells, presumably to compensate for a potential osmotic disturbance. There is another change perhaps to be classified as an electrolyte disturbance, a decrease in ammonia excretion. It is not wholly established yet whether this decrease is due primarily to a failure of elaboration of ammonia in the kidney in acute adrenal insufficiency or whether it is in some way related perhaps to anoxic changes of the kidney from decreased blood flow.

Turning now to the known adrenal cortical steroids and their physiologic effects, approximately thirty different steroids, all containing the so-called cyclopentanoperhydrophenanthrene nucleus, have been isolated from the adrenals. (Fig. 1.) They may be classified chemically as follows: (1) Steroids of the C_{21} pregnane group, containing 21 carbon atoms of which 17 comprise the cyclopentanoperhydrophenanthrene nucleus, 2 represent methyl groups attached to C-10 and C-13 respectively, and 2 represent the side chain at C-17. These have either 2,3,4 or 5 oxygen atoms and include 17-hydroxycorticosterone (Compound F), 17-hydroxy-11-dehydrocorticosterone (Compound E), 11-dehydrocorticosterone (Compound A), corticosterone, desoxycorticosterone and progesterone. (2) The C_{19} etiocholane group, containing 19 carbon atoms (no side chain at C-17). These include androstane-11-diol-17-one and andrenosterone. (3) Phenols-estrone.

The relation between the structure of the different steroids and their physiologic

activity is of interest. The steroids isolated from the adrenals may be classified in this respect as follows: (1) Steroids which affect salt and water metabolism; (2) steroids which affect carbohydrate and protein metabolism; (3) steroids which are definitely androgenic; (4) steroids which are definitely estrogenic; (5) steroids which are progestational in their activity and (6) the inactive steroids, those which as far as we know have no physiologic activity at all.

Desoxycorticosterone is distinguished by its striking effects on salt and water metabolism. The steroids with an oxygen at C-11, on the other hand, have significant effects on carbohydrate and protein metabolism (Fig. 1); those 11-oxysteroids possessing in addition an hydroxy group at C-17 have an even more striking effect, particularly 11-dehydro-17-hydroxycorticosterone, known as Compound E of Kendall. About equal in potency is 17-hydroxycorticosterone (Kendall Compound F). Next down the scale of activity is corticosterone, which has an hydroxy group on C-11 but no C-17 hydroxy group. Still less active is 11-dehydrocorticosterone (Kendall Compound A) which still has some carbohydrate and protein effects readily demonstrable in small animals and also (in the experience of Drs. Thorn, Perera, Kepler and others) slight salt and water effects in man. Desoxycorticosterone, which has neither an oxygen at C-11 nor an hydroxy group at C-17 has, as I said, an insignificant effect on carbohydrate and protein metabolism but exhibits striking effects on the reabsorption of sodium by the renal tubules and augmentation of potassium excretion.

I have asked Dr. Knowlton to talk to us at greater length on the subject of the participation of the adrenals in carbohydrate and protein metabolism.

DR. ABBIE I. KNOWLTON: Dr. Loeb has told you that as long ago as 1909 Porges reported the occurrence of hypoglycemia in adrenalectomized animals. Although this observation was made forty years ago, the influence of the adrenals upon carbohydrate metabolism is still under investigation.

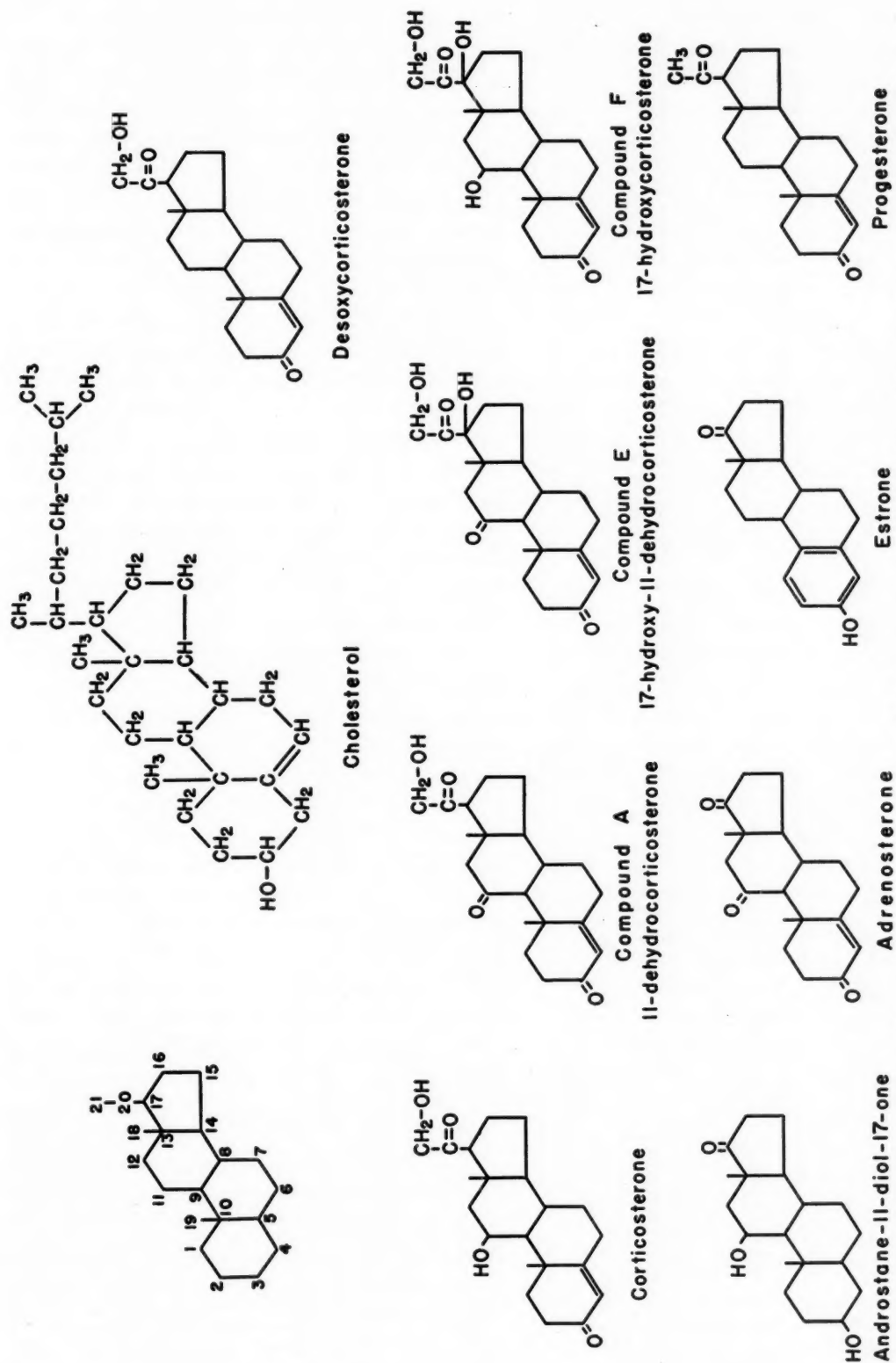


FIG. 1. Structural formulas of some adrenal cortical steroids. Upper left, the cyclopentanoperhydrophenanthrene nucleus, indicating the numbering of the carbon atoms, with substituent bonds to indicate the positions of C-18, C-19, C-20 and C-21. To the right, the full structural formula of cholesterol which the adrenal cortex can synthesize. Upper right, desoxycorticosterone, a C₂₁ compound with the pregnane grouping (in this and all subsequent formulas the methyl groups on C-10 and C-13 are indicated only by a bond). Second row: Four C₂₁ compounds with the pregnane grouping in which an oxygen is present in the C-11 position (C-11 oxysteroids). Third row: Androstane-11-diol-17-one and adrenosterone are C₁₉ compounds with the etiocholane grouping. Estrone is a C₁₈ phenol. Progesterone is a C₂₁ compound with the pregnane grouping.

The problem has presented considerable difficulty largely because many changes ensue following adrenalectomy, particularly those resulting from abnormal electrolyte balance, which may indirectly affect carbohydrate and protein metabolism. To separate these "non-specific" changes from those which may be termed "specific" has required careful study. It has required, further, studies on experimentally adrenalectomized animals in which the electrolyte disturbances have been corrected. Fortunately, at least in the rat, mouse and dog, this can be achieved by the liberal use of sodium chloride without resort to adrenal hormone substitution therapy. Ingle has emphasized the importance of such studies and in a recent review¹ gave the following three examples in which "non-specific" changes may reflect upon carbohydrate and protein metabolism.

First of all, the animal without its adrenals, unless treated, eats less than the normal animal. This may follow in large part from changes in electrolyte balance which result in dehydration, nausea and frequently vomiting. Secondly, these changes may affect absorption. In studies on the absorption of carbohydrate from the intestinal lumen, Wilbrandt and Lengyel working in Verzar's laboratory originally claimed that the adrenal cortex had an accelerating effect upon the phosphorylating processes in the gut. They demonstrated a markedly reduced rate of glucose absorption from the gut in adrenalectomized animals. However, subsequent workers have shown that if the animal is maintained on adequate amounts of sodium chloride and water, absorption of sugar proceeds at a quite normal rate. Thirdly, in 1940 Long, Katzin and Fry² pointed out that hypoglycemia and reduction in liver glycogen content did not occur in adrenalectomized rats and mice if the

animals were given access to food and salt, and that it is only under the stress of fasting that these abnormalities developed.

So much for the "non-specific" changes in carbohydrate metabolism seen after adrenalectomy. Let us consider now the evidences for a more specific action of the adrenal cortex upon these phases of metabolism. It was Long and Lukens who first demonstrated in 1934 that the insulin requirement of a diabetic dog was much reduced following adrenalectomy. Six years later Long et al.² showed in similar experiments upon diabetic rats that adrenalectomy resulted in a disappearance in glycosuria although once the animals continued to gain weight this could not be attributed to non-specific effects resulting from altered food intake or electrolyte imbalance. In addition they reported that the administration of adrenal cortical extracts led to a reappearance of urine sugar. These investigators and Wells and Kendall performed similar studies using single cortical steroids and, as Dr. Loeb has told you, found that the C₂₁ steroids which possess an oxygen atom in the 11 position (Fig. 1) all exhibit an effect upon carbohydrate metabolism. Of these Compound E of Kendall appears to be the most active and with daily injections of this steroid Ingle in 1941 reported the induction of glycosuria in normal force-fed rats. In diabetic Addisonians Thorn and Clinton³ and Sprague and Keppler⁴ both found that the use of Compound E resulted in increased glycosuria; however, in non-diabetic patients with Addison's disease Sprague et al.⁵ and Perera et al.⁶ have found disappoint-

¹ INGLE, D. J. The Physiological Action of the Adrenal Hormones. The Chemistry and Physiology of Hormones. Pp. 83-103, 211-243. Washington, D. C., 1944. The American Association for the Advancement of Science.

² LONG, C. N. H., KATZIN, B. and FRY, E. G. The adrenal cortex and carbohydrate metabolism. *Endocrinology*, 26: 309, 1940.

³ THORN, G. W. and CLINTON, M., JR. Metabolic changes in a patient with Addison's disease following the onset of diabetes. *J. Clin. Endocrinol.*, 3: 335, 1943.

⁴ SPRAGUE, R. G., KEPLER, E. J., KEATING, F. R., JR. and POWER, M. H. Coexisting Addison's disease and diabetes mellitus: comparative effects of Compound E (17-hydroxy-11-dehydrocorticosterone) and allied substances in 3 cases. *J. Clin. Investigation*, 26: 1198, 1947.

⁵ SPRAGUE, R. G., GASTINEAU, C. F., MASON, H. L. and POWER, M. H. Effects of synthetic 11-dehydrocorticosterone (Compound A) in a subject with Addison's disease. *Am. J. Med.*, 4: 175, 1948.

⁶ PERERA, G. A., PINES, K. L., HAMILTON, H. B. and VISLOCKY, K. *Am. J. Med.*, 7: 56, 1949.

ingly little evidence of an alteration in carbohydrate metabolism. This may be said also for the use of whole adrenal extracts which in adrenal insufficiency in man produce no quantitatively significant effect upon fasting blood sugar or glucose tolerance curves. Since such extracts have an unequivocal effect in small animals, this lack of effect in the human may be a matter of dosage.

Within the last two years further evidence of the influence of the adrenals upon carbohydrate metabolism has been obtained with the use of the adrenal stimulating hormone of the pituitary—adrenocorticotrophic hormone (ACTH). In studies on normal humans receiving this substance, Mason et al.⁷ reported increased insulin resistance, Forsham et al.⁸ demonstrated some impairment of glucose tolerance, and Conn, Louis and Wheeler⁹ and also McAlphine et al.¹⁰ observed a heavy glycosuria.

As to the source of the increased carbohydrate which was observed following the injection of adrenal cortical extracts, Long et al. postulated that this was derived by gluconeogenesis from protein catabolism. However, these authors also observed that a decreased proportion of glucose was being oxidized and this now is considered the more important action. Ingle has shown that the glycosuria which occurs during the administration of Compound E is far in excess of the amount which would be expected were it derived from the breakdown of protein. Similarly, in humans receiving ACTH Conn

has observed significant glycosuria in the absence of a negative nitrogen balance. To explain such observations Ingle has postulated that the adrenal cortical hormones decrease carbohydrate utilization. An argument in favor of decreased utilization is the extraordinary resistance of Compound E-treated rats to insulin (up to 1,000 units without control of glycosuria). Similarly, Conn has reported the administration of 100 units of insulin to a normal patient receiving ACTH without control of the hormone-induced glycosuria. These findings are in accord, too, with the work of Cori¹¹ who has shown, *in vitro*, that adrenal cortical extract in the presence of anterior pituitary extract has an inhibitory effect on the initial step of glucose utilization, i.e., the conversion of glucose to glucose-6-phosphate, the step which involves the enzyme hexokinase. Insulin in this *in vitro* system acts to release the inhibition produced by these hormones.

As to the effect of the adrenals upon protein metabolism, I have already mentioned Long's contention that the C-11 oxysteroids increase the breakdown of protein and its conversion to carbohydrate. Dougherty and his group have shown that following injections of adrenocorticotrophic extracts a marked dissolution of certain body proteins, i.e., lymphoid tissue occurs. More recently Forsham et al. have pointed out a striking fall in circulating eosinophiles following the injection of adrenal hormones of the C-11 oxysteroid group or of ACTH.

Studies of these hormones have shown that they cause inhibition of growth in immature animals and may actually cause a loss of weight in adult animals. This could in part be considered the result of reciprocal action of these hormones on the pituitary gland causing depression of activity. However, Marx, Simpson and Evans in 1943 reported that ACTH counteracted the effects of growth hormone in hypophysectomized rats.

¹¹ CORI, C. F. Enzymatic reactions in carbohydrate metabolism. Harvey Lectures. Series XLI, p. 253, 1945-46.

⁷ MASON, H. L., POWER, M. H., RYNEARSON, E. A., CIARAMELLI, L. C., LI, C. H. and EVANS, H. M. Results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 1, 1948.

⁸ FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G. and HILLS, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.*, 8: 15, 1948.

⁹ CONN, J. W., LOUIS, L. H. and WHEELER, C. E. Production of temporary diabetes mellitus in man with pituitary adrenocorticotrophic hormone; relation to uric acid metabolism. *J. Lab. & Clin. Med.*, 33: 651, 1948.

¹⁰ McALPINE, H. T., VENNING, E. H., JOHNSON, L., SCHENKER, V., HOFFMAN, M. M. and BROWNE, J. S. L. Metabolic changes following the administration of pituitary adrenocorticotrophic hormone (ACTH) to normal humans. *J. Clin. Endocrinol.*, 8: 591, 1948.

It cannot be said that the adrenal cortex is essential for protein breakdown or for its conversion to sugar. Wells and Kendall in 1940 reported that phlorhizinized adrenalectomized rats fed casein were able to metabolize this protein and excrete amounts of glucose and nitrogen quite comparable to those excreted by similarly treated rats with intact adrenals. This is a further argument against the view that the adrenals have a major action on deamination of protein or on its conversion to glucose. More recently Ingle and Oberle have reported that following adrenalectomy rats excrete nitrogen in amounts comparable to sham-operated control animals.

We might return now to the clinical symptoms of hypo- and hyperadrenalism listed in Table 1. From what has been said, we might expect hypoglycemia to occur in patients with Addison's disease, especially after periods of decreased food intake. Approximately one-third of the patients studied in this hospital have symptoms referable to hypoglycemia while the majority will have occasional blood sugars below 70 mg. per cent. Frequent feedings or, in crises, liberal parenteral glucose remains the chief method of combating this disturbance since little effect upon this phase of metabolism has been demonstrated with either whole adrenal extracts or single steroids in humans. In Cushing's disease, on the other hand, decreased carbohydrate tolerance is the rule and frequently frank diabetes exists. In these patients assays of the urine for material having "corticoid" activity have been made and, as might be expected, increased amounts are present, the reverse being true in Addison's disease. Albright has postulated that the observed osteoporosis in Cushing's disease results from an abnormality in protein metabolism. Perhaps the increased bruising tendency may fit here, too. The change in body form, the "moon facies" and increased neck and

¹² Li, C. H., SIMPSON, M. E. and EVANS, H. M. Influence of growth and adrenocorticotrophic hormones on the body composition of hypophysectomized rats. *Endocrinology*, 44: 71, 1949.

upper thorax obesity may be related to the observation of Li et al.¹² that animals receiving ACTH show an increased deposition of fat in place of protein.

In recapitulation, I think we can say that the adrenals, by virtue of their elaboration of C-11 oxysteroids, do have demonstrable effects on both carbohydrate and protein metabolism. However, I think the point which Dr. Loeb mentioned at the beginning, that the hormones do not initiate but simply facilitate or otherwise alter existing body reactions, must be remembered. The adrenalectomized animal can metabolize carbohydrate normally provided it is kept on an adequate salt intake and not subjected to stress. Likewise, protein turnover can proceed in the absence of the adrenals, as witness the growth of adrenalectomized rats maintained on sodium chloride and the elaboration of antibodies in the absence of adrenal glands (indicating anabolism) and, on the other hand, the quite normal nitrogen excretion reported by Ingle following adrenalectomy (indicating catabolism).

DR. LOEB: In addition to the steroids which are concerned with salt retention and carbohydrate and protein metabolism, some are related very closely to sex hormones and these will be discussed by Dr. Jailer.

DR. JOSEPH W. JAILER: As Dr. Loeb indicated, about thirty different steroids have been isolated from the adrenal cortex so that while the adrenal cortex may not be the seat of the soul it is certainly the stockpile of the steroids. A number of these show estrogenic or androgenic activity. Of the 17-ketosteroids excreted by normal individuals, approximately 60 per cent are of adrenal origin. However we do not know what role they play in the normal individual. It has been shown that adrenalectomized animals maintained on desoxycorticosterone or salt and water may show perfectly normal estrus cycles and if maintained in good condition conceive and go through pregnancy. In fact, it has been shown that in some species it is easier

to maintain a pregnant adrenalectomized animal than an adrenalectomized animal which is not pregnant. When the animal becomes sick, the estrus cycles cease and the animal shows evidence of either estrogen or androgen withdrawal. In the female Addisonian patient menstrual periods occur normally so long as the patient remains generally well. In fact, we have in our records at the Presbyterian Hospital six pregnancies in patients with Addison's disease.

In the so-called Cushing syndrome the bulk of the adrenal steroids excreted in the urine are of the 11-oxygenated corticosteroid group. Occasionally, however, there may be increased excretion of the 17-ketosteroids, which have been isolated by several workers. Mason and Keppler at the Mayo Foundation have shown that although no physiologic manifestations of hyperandrogenism develop, androgens are found in the urine. It is in another adrenal syndrome, the so-called adrenogenital syndrome, however, that a marked increase in the excretion of 17-ketosteroids occurs. We can quote two examples from our own cases. There were two patients at the Babies Hospital quite recently, one child of six and one-half years and the other about seven years, ages in which approximately 2 mg. or so of 17-ketosteroids ordinarily are excreted daily; one excreted 175 mg. and the other 189 mg. of 17-ketosteroids. Both had adrenal tumors verified at operation.

DR. LOEB: I think it important to emphasize that adrenal cortical extract as prepared from adrenal glands does not give rise in animals to manifestations of the adrenogenital syndrome but when given in excess will produce many manifestations that one encounters in Cushing's syndrome. Thus we have some evidence to indicate that many of the manifestations of Cushing's syndrome of adrenal origin result from excessive elaboration of normal steroids whereas, as Dr. Jailer has intimated, the steroids which are elaborated in patients with the adrenogenital syndrome are, per-

haps, either qualitatively or quantitatively different. We know that abnormal steroids are excreted in the urine of some patients, in others the "target" organ is perhaps more sensitive to normal steroids with estrogenic or androgenic activity. This is a very inadequate discussion of the subject but we cannot cover the entire field in the time allotted.

STUDENT: What are corticoids?

DR. JAILER: The term "corticoids" refers to substances of undefined chemical structure (some doubtless steroids) which are present in the urine and exhibit biologic activity similar to that of certain cortical steroids. They are capable of increasing glycogen storage in young adrenalectomized rats and are protective upon exposure to cold, in the manner of adrenal cortical extract. Increased amounts of corticoids appear in the urine of subjects exposed to various kinds of stress and in the urine of patients with Cushing's syndrome.

STUDENT: Would you comment on the effects of Compound E and ACTH in rheumatoid arthritis and acute rheumatic fever?

DR. LOEB: Nothing now known about the metabolic effects of these substances would account for the striking temporary remissions they produce in rheumatoid arthritis and rheumatic fever. This is, for the present, a completely obscure phase of the role of the adrenal glands.

We now come to another uncertain chapter, namely, that concerning pigmentation. Pigmentation frequently is a prominent feature in the Addisonian patient, but there are a certain number of patients with total destruction of the adrenal glands who never develop pigmentation. It has been my impression that those who never develop pigmentation are the red-haired individuals who, perhaps, have not the cells in their skin which are capable of elaborating pigment normally. Dr. Cross might comment on this.

DR. RICHARD J. CROSS: The chief work in this field has been done by Ralli and her co-workers who became interested in reports of changes in pigmentation of

animals following adrenalectomy. They proceeded to study this phenomenon in pantothenic acid-deficient rats. As you know, the hair of black or brown rats kept on diets deficient in this vitamin turns gray and grows very poorly. It was found that if such rats had their adrenals removed a luxuriant growth of pigmented hair occurred even though the deficient diet was continued. This phenomenon was further investigated by chemical analyses of the pelts of these rats for the various substances known to play a part in melanin formation but so far it has not been possible either to localize the block present in the pantothenic acid-deficient rat or determine how adrenalectomy removes this block. It was found that if the adrenalectomized rats were maintained on desoxycorticosterone, the return of pigmentation did not occur. The same was true to a lesser extent when adrenal cortical extract was administered.

It is tempting to conclude from this that there is a reciprocal relationship between pantothenic acid and desoxycorticosterone as far as melanin formation is concerned. However, the problem is more complicated than this and at present the exact nature of the connection between adrenal cortical function and pigment metabolism, and to the pigmentation of Addison's disease is still not known.

DR. LOEB: While it is possible to keep the adrenalectomized animal alive by maintaining an adequate circulation, the adrenalectomized dog maintained on salt and water can hardly be described as a "fighting cock," and in times of stress the animal is wholly incapable of meeting physiologic demands. As you know, the relation of stress to adrenal cortical activity has been given considerable prominence in recent years through the studies of Weil and Browne, who demonstrated so-called corticoids in the urine following stress; and particularly by Selye in Montreal who introduced the concept of alarm reaction and adaptation syndrome in relation to adrenal cortical activity. I am going to ask Dr. Perera to summarize briefly the

so-called alarm reaction and adaptation phenomena as visualized by Selye.

DR. GEORGE A. PERERA: The adrenal cortex has long been known to have certain emergency functions. These are not only related to carbohydrate metabolism and hypoglycemia and, as Ingle has shown, to the capacity to perform muscular work but many investigators have commented on the vulnerability of adrenalectomized animals to many forms of stress, i.e., cold, anoxia, hemorrhage, burns and sensitivity to certain drugs such as morphine and histamine. Weil and Browne noted that following acute infections or after operative procedures, materials were excreted in the urine which prolonged the survival of adrenalectomized rats exposed to cold. It has also been observed that after stress of many types increased corticoid materials are excreted which augment the storage of glycogen in the fasted adrenalectomized animal.

The term homeostasis has been given to many reactions of adjustment to environmental change; others applied different designations to these phenomena; and Selye summarized the response to stress under the "alarm" reaction. He defined this pattern as the "sum of all of the biological phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted."

Selye found, as others had previously described in part, that many changes took place when the individual or the animal was exposed to stress. First a shock phase appeared during which the following were among the alterations noted: tachycardia, decreased muscle tone, decreased body temperature, ulcer formation in the gastrointestinal tract, hemoconcentration, anuria, edema, decreased blood chlorides, acidosis, a rise in blood sugar followed by a fall, leukopenia and then leukocytosis, increased liberation of epinephrine, decrease in blood clotting time, in fact, almost every organ and system appeared to be involved. This reaction was followed by a countershock phase, during which period there developed

enlargement of the adrenal cortex and evidence of increased activity of its cells. In addition, there was an acute involution of the thymus, of lymph nodes and of the pancreas. Degranulation of the hypophysis was observed, and during the countershock phase a reversal of most of the signs and symptoms took place that had appeared during the shock phase. Following shock and countershock a stage of resistance was described and then, if the stress was severe or prolonged, a final stage of exhaustion.

As an outgrowth of these observations Selye formulated the concept of a "general adaptation syndrome" which he defined as the "sum of all non-specific systemic reactions of the body which ensue upon long continued exposure to stress." He found, for example, that removal of the hypophysis or the cortex of the adrenals exaggerated the shock phase and rendered the countershock phase negligible or even absent. He showed in various animal species that stress of many types or the administration of large doses of desoxycorticosterone together with salt could produce an assortment of diseases and disorders. Under these conditions hypertension might develop. Lesions appeared which were similar to nephrosclerosis, periarteritis nodosa, acute rheumatic fever and rheumatoid arthritis.

From these results Selye postulated a group of disorders which he termed "diseases of adaptation" and suggested that they may arise even in man, due to inability of the organism to adjust properly to stress. Because of the fact that these disorders could not be produced after hypophysectomy or adrenalectomy, he developed a scheme to the effect that alarm produces certain catabolic impulses; these in turn affect the hypophysis and the adrenal cortex through the adrenocorticotrophic hormone; the adrenals modify carbohydrate metabolism, perhaps also the action of the thymus and lymphatic system and hence the production of antibodies; finally, such disorders as hypertension are produced by the effect of hormones of the adrenal cortex through a

cycle involving the kidneys and renin production.

No one can deny that alarm or stress in almost any species causes a major sequence of events involving practically every system, organ and tissue of the body. On the other hand, we must regard the concept of these "diseases of adaptation" as interesting but highly speculative. Attempts to reproduce some of the disturbances described by Selye, perhaps under conditions that were not quite identical, have not given comparable results. It has been pointed out that epinephrine is a potent stimulus to the adrenal cortex as demonstrated by the fact that there is a decrease in the ascorbic acid and cholesterol content of the adrenal cortical cells. An increase in corticoids in the adrenal veins was observed by Vogt. It now seems probable, as stated by Long and Sayers, that the action of epinephrine on the adrenal cortex is governed through its effect on the hypophysis.

In conclusion, we must accept the "alarm reaction" and the resultant phenomena produced; we must admit that in some way the hypophysis and the adrenal cortex may be concerned in this reaction; but we are still obliged to hold reservations regarding the concept of "diseases of adaptation." There is abundant evidence indicating that the adrenal cortex, although concerned in the "alarm reaction," may not be essential for all of the signs and symptoms which follow stress.

DR. LOEB: It is undeniable that the adrenal cortex plays a very active part in responses to stress. This is demonstrated first by the fact that the adrenalectomized animal is unable to withstand stress, and second by the fact that many forms of stress are associated with rapid depletion of the ascorbic acid content of the adrenal cortex, an important component of the adrenal cortex, and also with rapid depletion of the cholesterol content of the adrenal cortex which presumably is related somehow to synthesis of physiologically active steroids in the body. I think Dr. Perera and some of the rest of us have misgivings concerning

the concepts of Selye in that we believe that structure and functions other than those referable to the adrenal cortex may be involved in response to stress such as cold, burns, surgical operation, infections, etc. Also, the evidence which Selye offers for adrenal overactivity as the cause of rheumatic fever, appendicitis, tonsillitis and other disorders is not wholly convincing.

The next aspect of adrenal cortical function which will be discussed is one which has aroused considerable interest and is of considerable importance, namely, that of the role of the adrenal cortex in infection and resistance to infection. At the outset, I should like on purely clinical grounds to state that I do not subscribe to the thesis often propounded that patients with Addison's disease are more prone to infection than are patients with intact adrenal glands. This idea of increased susceptibility probably arises from a fact which I think is incontrovertible, namely, that the patient with Addison's disease or the adrenalectomized animal is much less in a position to cope with severe infection than is the patient or animal with adrenal glands intact, but that is a far cry from saying that susceptibility to infection is greater in the absence of the adrenals. Dr. Eisen is going to summarize for us briefly his views concerning the relationship of the adrenal cortex to antibody production and release.

DR. HERMAN N. EISEN: The idea that adrenal cortical steroids regulate the production and distribution of antibodies is based upon two beliefs: (1) that lymphocytes actually produce antibodies and gamma globulin or at least constitute a significant reservoir for these proteins, and (2) that lymphocytes readily undergo lysis upon exposure to excessive amounts of adrenal cortical steroids, thereby contributing their antibody and gamma globulin content to the blood plasma.

The evidence in support of an adrenal cortical influence on fixed and circulating lymphocytes is well established: The administration of adrenal cortical steroids or of adrenocorticotrophic hormone (ACTH)

causes a pronounced lymphopenia in blood and striking fragmentation of tissue lymphocytes with reduction in the size of lymph nodes and thymus. Furthermore, in animals and in man adrenal insufficiency is characterized by blood lymphocytosis and by a relative increase in weight of lymph nodes and thymus. The latter effects, incidentally, are commonly but mistakenly referred to as lymphoid and thymus hyperplasia. As has been shown by Dr. Herbert Stoerk, the increase in weight of the thymus in animals deprived of their adrenals is merely an approximation of the weight attained by this tissue in normal animals living under optimal conditions, i. e., in adrenalectomized animals involution of lymphoid tissue is reduced to a minimum but no true hyperplasia exists. It is interesting to note in this connection that a similar reduction in involution of lymphoid tissue (i.e., relative "hyperplasia") occurs in gonadectomized animals whose adrenals are intact, indicating that perhaps gonadal steroids also have an effect on lymphocyte dissolution.

In contradistinction to the foregoing facts, the evidence in support of the belief that lymphocytes actually form or accumulate antibodies remains controversial. It has been suspected for fifty years and perhaps longer that lymph nodes have something to do with the formation of antibodies. Few if any clear-cut experiments were done, however, until about ten years ago when McMaster and Hudack performed the following experiment: The ears of mice were injected several times intradermally, the left ear receiving antigen A and the right ear receiving antigen B. Eight days after the last injection the serum had anti-A and anti-B agglutinins; extracts of those cervical lymph nodes which drained the left ear had relatively large amounts of anti-A but very little anti-B agglutinins, whereas similar extracts of those cervical lymph nodes which drained the right ear had relatively large amounts of anti-B but very little anti-A agglutinins. Amputation of the ears two hours after inoculation with antigen did not alter the results. This experiment

indicates that the regional lymph nodes which drain a skin site that has been injected with antigen probably forms antibody. However, as McMaster and Hudack pointed out, their results do not indicate that lymph nodes are the exclusive or even the chief site of antibody formation. And, what is more relevant to this discussion, their results do not indicate which of the several types of cells in the lymph node is responsible for antibody production. Sabin's evidence suggests that this process may be localized in the large phagocytic macrophages. More recently a number of Scandinavian workers have focused attention upon plasma cells as a possible site of antibody formation. But from the viewpoint of adrenal cortical participation the possible role of the lymphocyte is most significant since it is specifically these cells that are shattered so conspicuously by adrenal cortical steroids.

Harris and Ehrlich in an extensive series of experiments found that following the injection of antigen into the hind foot pad of rabbits the popliteal lymph nodes draining this area became enlarged and exhibited considerable lymphocyte hyperplasia. These investigators then separated lymphocytes from the lymph in the efferent lymphatic emerging from these nodes and found that extracts of these lymphocytes had antibody titers which were about seven times greater than that of the lymph from which they had been separated. It was concluded that the lymphocytes actually formed antibody. The conclusion reached was dependent upon the validity of the quantitative differences observed between lymphocytes and lymph. Despite the considerable care exercised in these experiments it has not yet been shown experimentally that the technics used are sufficiently sensitive and accurate to validate the conclusions drawn.

As you are all aware, Dougherty and White have recently attempted to demonstrate a relationship between adrenal cortical steroids, lymphocytes and antibodies. These workers immunized animals, allowed them to rest until serum antibody titers were

very low or no longer detectable, then administered ACE or ACTH, or substances which provoke increased adrenal cortical activity, and in each instance observed, concomitantly with fragmentation or lymphocytes, sharp rises in the serum antibody titers. However, a number of more recent efforts to extend these results have not confirmed the fact that massive lysis of lymphocytes in immunized animals leads to augmentation of serum antibody concentrations. In addition, a number of reports in the literature, as well as our own experiments, indicate that adrenalectomized rats and rabbits have, after immunization, serum antibody levels that are about the same as those of intact control animals similarly immunized. Indeed in some of the older reports, as well as in a recent publication by Murphy and Sturm, adrenalectomized animals are recorded as having antibody levels that are higher than those of controls but, since the possibility of hemoconcentration in the adrenalectomized animals had not been considered, such reports of elevated titers cannot be accepted. In other experiments, a group of us have found identical serum antibody and γ -globulin concentrations in (1) adrenalectomized rats which were maintained on DCA and NaCl but, lacking other cortical steroids, had as a consequence the anticipated large amount of intact lymphoid tissue and in (2) similar rats (i.e., adrenalectomized animals maintained on DCA and NaCl) given ACE and having as a result considerably reduced amounts of lymphoid tissue. These results seemed to indicate that extensive lymphocyte dissolution, induced by ACE, did not measurably contribute to serum antibody and gamma globulin levels. The possibility that such a contribution might actually have occurred but was obscured because ACE simultaneously enhanced the rate of antibody and gamma globulin degradation, along with the catabolism of other proteins, was considered but rejected after it was found that ACE had no measurable effect in adrenalectomized rats on the turnover of serum

proteins as determined through the use of heavy nitrogen (N^{15}).

Since massive lymphocyte dissolution induced by ricin, ACTH, ACE, etc., does not measurably elevate serum antibody levels, it appears that lymphocytes are not a significant reservoir for antibodies. Furthermore, the experiments reviewed indicate that the adrenal steroids do not exert a major influence upon the production or the distribution of antibody. These negative results, however, do not exclude the possibility that lymphocytes may contain a small amount of antibody which, under special circumstances that have not yet been defined, may be liberated to produce detectable augmentation of serum antibody concentration. Such a possibility would be compatible with the negative evidence accumulated above if the antibody content of lymphocytes were small relative to the total body antibody content. However, in this event the influence of the adrenal cortex on antibodies would nevertheless remain of quite minor significance.

STUDENT: Dr. Loeb, would you summarize the principles to be followed in the management of Addison's disease?

DR. LOEB: Treatment should be directed toward correcting, as far as possible, the metabolic defects present. The disturbances resulting from defects in water and electrolyte metabolism are relatively easily controlled. The disturbances in carbohydrate and protein metabolism are less amenable to therapy. The effects of stress resulting from surgical procedures and infection are still less satisfactorily controlled with the result that a number of patients continue to succumb rather suddenly even when defects in electrolyte and carbohydrate metabolism are not apparent.

A number of patients with documented Addison's disease live and work and maintain relatively good health for many years on a regimen of 10 to 20 Gm. of sodium chloride daily in addition to the salt in their diet. The majority require small doses of desoxycorticosterone in addition to a liberal salt intake. In view of the fact that this

steroid in therapeutic dosage is believed to exert an effect only on electrolyte metabolism, it is of more than passing interest that most patients treated with DCA are able to carry on a relatively normal existence and exhibit only occasional hypoglycemic episodes. In patients with recurrent symptoms of hypoglycemia little is to be gained by the daily injection of cortical extract. Indeed, even the 11-oxysteroid Compound A of Kendall in doses of 60 mg. daily has an inappreciable effect on blood sugar in these patients. Furthermore, Compound E of Kendall, which has a striking effect on glycogen storage in the rat and which intensifies diabetes in the human, in doses of 80 mg. daily has only a slight effect on the blood sugar of the Addisonian. The most satisfactory control of hypoglycemia in these patients is achieved by frequent feedings during the day and a feeding at bedtime.

In the treatment of acute crises, infusions of saline and glucose supplemented with desoxycorticosterone usually re-establish adrenal compensation. In the presence of fever or surgical intervention we have gained the clinical impression that the injection of 5 cc. of hog adrenal "lipo-extract" every eight hours and transfusion are effective adjuvants to the other measures mentioned.

SUMMARY

DR. FREDERICK K. HEATH: While the endocrine glands are not essential to living processes, they do coordinate these in the complex organism and so render it more adaptable to stress. Without an endocrine system the organism can survive often only under special conditions.

About one hundred years ago Addison first reported death following total destruction of the adrenal glands but the importance of the cortical tissue was not emphasized until almost fifty years later and then by the failure of epinephrine to support life in the total absence of the whole glands. Now, with some thirty different cortical steroids isolated, it is possible in

part to correlate cortical functions with specific chemical structure.

Substances having effects upon salt and water exchange, and carbohydrate and protein metabolism are found in the pregnane group of steroids with 21 carbon atoms. The androgenic substances fall into the class with no side chain at C-17 and therefore belong to the etiocholane group with 19 carbon atoms. Estrogenic materials are found in the phenols with 18 carbon atoms.

Control of the electrolyte balance, so far best understood of the cortical functions, was in large part worked out before the active steroids were available. It is now known that desoxycorticosterone (and to a small extent 11-dehydrocorticosterone) act upon the renal tubular cells so as to promote the reabsorption of sodium and the excretion of potassium. Individuals with Cushing's syndrome may have high serum sodium and low serum potassium levels and tend toward hydremia and hypertension. The Addisonian, on the other hand, tends toward low sodium and high potassium concentrations in the serum, dehydration and hypotension; as the tubules fail to reabsorb sodium and retain potassium, there is a loss of chloride and/or bicarbonate, nitrogen retention and a fall in urinary ammonia. The administration of salt and water with or without DCA usually reverses this trend and relieves the accompanying symptoms.

Hypoglycemia occurs in the adrenalectomized animal. Conversely, the diabetic animal is relieved by adrenalectomy and is made worse by the administration of either cortical extract or the 11-oxysteroids, particularly 11-hydro-17-hydroxycorticosterone (Compound E of Kendall). Cori offers an explanation of these findings, which are associated with decreased phosphorylation of glucose, by the *in vitro* demonstration that cortical extract increases the inhibitory effect of anterior pituitary extract on hexokinase, an inhibition antagonized by insulin.

Low blood sugar, episodes of hypoglycemia and insulin sensitivity may occur

in the Addisonian patient. Yet to date, except in hypoadrenalism with diabetes or diabetes alone, no significant effects upon carbohydrate metabolism have followed the use of any adrenal cortical substance in humans. In contrast, ACTH does exert an appreciable effect in normal man. Diabetes and insulin resistance may be seen in instances of hyperadrenalism.

The effect of the adrenal cortex upon protein metabolism is obscure. The gluconeogenic effect appears to be less than that upon carbohydrate utilization. In small animals the 11-oxysteroids seem to cause inhibition of growth during the growing phase and weight loss in mature animals.

Decreased excretion of the urinary corticoids and 17-ketosteroids occurs after adrenalectomy and in Addison's disease. Increased excretion of these compounds may be found in hyperadrenalism. There is a marked increase in 17-ketosteroid excretion in the adrenogenital syndrome which may represent the formation of abnormal steroids.

In this connection the increased urinary excretion of corticosteroids of the 11-oxy group following exposure of normal animals to stress, substances which serve to protect an adrenalectomized animal under similar conditions, introduces the concept of the "alarm" reaction, "general adaptation syndrome" and the "diseases of adaptation" of Selye. The opinion was expressed that these hypotheses required more verification.

The effect of adrenal cortical materials on antibodies is probably small. No question exists as to the reduction in circulatory lymphocytes, fragmentation of tissue lymphocytes and reduction in the size of lymph nodes and thymus following the exhibition of cortical substances. On the other hand, no conclusive evidence establishes the lymphocyte *per se* as an important source of antibodies. Furthermore, adrenalectomized animals appear to form antibody as well as normal controls and no changes in immunity have been noted in Addison's disease or Cushing's syndrome.

Clinico-pathologic Conference

Progressive Hepatic Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. C., (No. 154252), a twenty-seven year old white single college instructor, was admitted to the surgical service of the Barnes Hospital for the first time on December 26, 1947, complaining of jaundice. The family history was of interest only in that one of her grandparents had died of diabetes. The patient stated that she had enjoyed fairly good health most of her life. She had had seasonal hay fever for many years and at the age of twenty-one had a respiratory infection with cough and fever. The illness was complicated by bilateral thrombophlebitis, and she had pain and swelling of her legs which forced her to remain in bed for five weeks. Subsequently, she had varicose veins and persistent swelling of the legs; frequently shallow ulcers developed on the inner aspect of either ankle. A year prior to entry she had a respiratory infection with cough and fever which lasted a few weeks. Otherwise, the systemic history was non-contributory.

Two months before entry the patient developed a "head cold and sore throat" which lasted approximately three weeks. Shortly thereafter her urine became dark. She developed slight nausea after meals, her sclerae were noted to be yellow and she began to have a low grade fever. She consulted her physician who found gastrointestinal roentgenograms and cholecystograms to be normal. The patient's icterus index was 22 units.

The jaundice gradually decreased and the urine became lighter in color. One week before admission, however, the jaundice

recurred, her urine again became quite dark and the patient was advised to enter the hospital. Aside from slight abdominal discomfort which occurred occasionally after eating she was relatively free from symptoms.

At the time of entry the temperature was 37°C., pulse 68, respirations 16 and blood pressure 100/70. The patient was well developed, well nourished and in no distress. The essential findings were mild icterus of the skin and mucous membranes, many varicosities of both legs with marked bilateral edema and large areas of hyperpigmentation about both ankles.

The laboratory findings were as follows: Blood count: red cells, 4,100,000; white cells, 3,850; hemoglobin, 12.9 Gm.; differential count: eosinophiles, 12 per cent; stab forms, 3 per cent; segmented forms, 34 per cent; lymphocytes, 49 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace; sugar, negative; bile, +; urobilinogen, positive in dilution of 1:64; centrifuged sediment, negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; total protein, 9 Gm. per cent; albumin, 4.3 Gm. per cent; globulin, 4.7 Gm. per cent; icterus index, 51 units; prothrombin time, 80 per cent of normal; bromsulfalein dye retention, 40 per cent in forty-five minutes; thymol turbidity, greater than 24 units; cephalin-cholesterol flocculation test, 3 plus. van den Bergh test: direct, 1.8 mg. per cent; indirect, 1.0 mg. per cent; total, 2.8 mg. per cent.

A diagnosis of acute catarrhal jaundice was made, and the patient was discharged

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from the hospital on December 31, 1947. She did not restrict her activities, but jaundice persisted and although she experienced no pain or other symptoms she was re-admitted to the surgical service on March 7, 1948. Her appetite had been excellent.

At that time the essential physical findings included icterus of the skin, sclerae and mucous membranes. There was a soft blowing grade I systolic murmur at the apex but no other murmurs were described. The liver edge was easily palpable 2 cm. below the costal margin and was described as sharp but not tender. The legs appeared as on the first examination. The patient was afebrile.

The laboratory data were as follows: Blood count: red cells, 3,640,000; hemoglobin, 11.1 Gm.; white cells, 5,000; differential count: essentially normal except for 6 per cent eosinophiles. Stool: guaiac, 1 plus; negative for sodium bilirubinate. Urinalysis: The routine tests were negative. Urobilinogen was not present in abnormal amount. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; sugar, 66 mg. per cent; total protein, 8.5 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 5.4 Gm. per cent; icterus index, 76 units; thymol turbidity, 68 units; cephalin-cholesterol flocculation test, 1 plus; prothrombin time, 38 per cent of normal. van den Bergh test: direct, 4.8 mg. per cent; indirect, 2.8 mg. per cent; alkaline phosphatase, 4 Bodansky units.

Shortly after admission an exploratory laparotomy was performed. The common bile duct was isolated and found to be normal in size. The liver and spleen were each four to five times normal size, and nodules about 1 to 1½ cm. in diameter were scattered diffusely over the entire liver. They were not described further. One, however, was removed for examination, a section of which was described by the surgical pathology department as being indicative of chronic hepatitis. It was also stated that there were dense infiltration of lymphocytic cells and the changes of early Laennec's cirrhosis. Postoperatively, the patient was given a high carbohydrate, high protein,

low fat, low salt diet with vitamin B complex, vitamin K, ammonium chloride and choline chloride, and she received one whole blood transfusion. She was discharged unimproved on March 25, 1948. Her red count was 3,052,000 and her hemoglobin was 11.9 Gm.

The patient was re-admitted to the surgical service on June 20, 1948. During the interval between admissions she had continued to feel quite well and had followed the therapeutic regimen outlined for her. The jaundice had fluctuated somewhat but she believed that it was less intense than it had been.

Physical examination again revealed moderate icterus. The liver edge could be felt 2 to 4 cm. below the right costal margin on deep inspiration. Edema of the legs was still present as before.

The essential laboratory data were as follows: Blood count: red cells, 4,310,000; hemoglobin, 12.6 Gm.; total protein, 6.6 Gm. per cent; albumin, 1.9 Gm. per cent; globulin, 4.7 Gm. per cent. van den Bergh test: sodium bilirubinate, 5.8 mg. per cent; bilirubinoglobin, 4.7 mg. per cent; total bilirubin, 10.5 mg. per cent; cephalin-cholesterol flocculation test, 4 plus; prothrombin time, 20 per cent of normal; thymol turbidity, greater than 24 units.

The patient was discharged on June 23, 1948, to continue the same therapeutic measures previously outlined. After she left the hospital she felt generally well and thought that her jaundice had diminished further. The swelling of her legs, however, increased and in addition she noted puffiness about the eyes and increased protuberance of her abdomen. About two weeks before her fourth admission a very large "black and blue" spot appeared on her left thigh, and the skin over the area "blistered." Similar smaller areas appeared over the right thigh and on both lower legs. Concomitantly, she began to note persistent bleeding from the nose and gums and also from hemorrhoids. Her temperature rose to 101°F., and mild night sweats developed. Two days before admission small raised

areas appeared over the neck, chest and buttocks and there was some stiffness of the joints. Her appetite had remained good.

She re-entered the hospital on July 19, 1948, at which time her temperature was 37.4°C., pulse 80, respirations 16 and blood pressure 120/68. The patient did not appear to be uncomfortable. There was marked edema of the lower extremities extending to the pelvis but no periorbital edema was recorded. A papular violaceous eruption with lesions 2 to 4 mm. in diameter was present over the chest and back. Some of these lesions were crusted. Over the left thigh there was a large ecchymosis measuring 10 by 20 cm. Superficially the lesion was gangrenous and blistered. Other swollen ecchymoses were present over both thighs and lower legs and there were small punched out ulcers about the left ankle. Moderate icterus of the sclerae, skin and mucous membranes was present. Clotted and crusted blood appeared in both nostrils. The gums bled easily. There was a rather harsh, high pitched systolic murmur over the entire precordium best heard along the left sternal border. The abdomen was protuberant; the flanks bulged and a fluid wave was demonstrable. The liver edge was questionably felt 4 cm. below the costal margin in the right mid-clavicular line. The spleen could not be palpated. Large, soft, inflamed external hemorrhoids were present.

The laboratory findings were as follows: Blood count: red cells, 2,950,000; hemoglobin, 8.4 Gm. per cent; white cells, 7,400; differential count: eosinophiles, 6 per cent; segmented forms, 72 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace; sugar, negative; centrifuged sediment, 20 to 30 white blood cells per high power field; bile, positive; urobilinogen, present in a dilution of 1:128. Stool: positive for stercobilin. Blood chemistry: non-protein nitrogen, 15 mg. per cent; sugar, 42 mg. per cent; total protein, 6.9 Gm. per cent; albumin, 1.8 Gm. per cent; globulin, 5.1 Gm. per cent; prothrombin time, 14 per cent of normal; van den Bergh test: direct, 3.9 mg. per cent; indirect,

3.6 mg. per cent; total, 7.5 mg. per cent; cephalin-cholesterol flocculation test, 4 plus; thymol turbidity test, 35 units; serum phosphorus, 4.9 mg. per cent; alkaline phosphatase, 6 Bodansky units. Electrocardiogram: left axis deviation. Roentgenogram of the chest: bilateral pleural effusion, small.

The patient was given increased carbohydrate in her diet and received serum albumin and intrahepatol followed by whole blood transfusions. During her first two weeks in the hospital several spontaneous ecchymoses appeared. The prothrombin time remained 15 per cent of normal. Two weeks after admission an infected hematoma on the left thigh ruptured and purulent material drained. The patient's temperature rose to 38°C., and she was given penicillin. A similar sequence of events occurred, the involved lesion being on the right thigh. One month after entry the patient's prothrombin time was 19 per cent of normal. The red cell count was 3,000,000 and her hemoglobin, 8.8 Gm. She continued to receive 10 cc. of intrahepatol three times weekly and large amounts of vitamin B complex and vitamin K parenterally. Complete liver function studies revealed that the cephalin-cholesterol flocculation test was 4 plus, thymol turbidity, 33 units; icterus index, 36 units, total protein, 6.5 Gm. per cent, albumin 1.8 Gm. per cent and globulin 4.7 Gm. per cent. The urine contained urobilinogen in a dilution of 1 to 40 and was negative for bile. A trace of bile was present in the stool. Two months after entry there was little change in either the physical condition or the laboratory findings except that the white blood cells in the urine had disappeared. At the time of discharge on October 5, 1948, the patient had lost 32 pounds. There was considerable improvement in the surgical lesions of the lower extremities and edema was diminished. Aside from the slight rise in temperature at the time of rupture of the lesions on her thighs the patient had been afebrile.

She returned home and for ten days her condition remained unchanged. Tenderness along the varicose veins of the left leg then

developed and red raised lesions appeared around the left ankle which subsequently became necrotic and drained purulent material. She began to have afternoon temperature elevation and signs of inflammation in the left thigh appeared. She had not, however, been troubled by additional abnormal bleeding. She was admitted for the last time on October 30, 1948.

Physical examination at that time revealed the temperature to be 39.5°C., the pulse 94, respirations 18 and blood pressure 100/70. The patient was lying flat in bed with her legs drawn up. Her skin was pale and sallow. The neck veins were prominent. There were a few ecchymotic spots over the thighs. Scleral icterus was slight. Edema was present in both lower extremities, particularly on the left, and a number of small ulcers surrounded the left ankle. There was a healing ulcer on the lateral aspect of the right thigh and on the anteromedial aspect of the left thigh; marked redness, tenderness and swelling were noted. The inguinal nodes were non-tender. Breath sounds were moderately impaired at the left base. A grade II, soft blowing systolic murmur was heard at the apex and the base. The liver edge was felt 4 cm. below the right costal margin in the mid-clavicular line; it was slightly tender. The spleen tip could be palpated when the patient took a deep breath.

Laboratory data were as follows: Blood count: red cells, 3,117,000; hemoglobin, 9.5 Gm.; white cell count, normal; differential: normal. Urinalysis: negative except for an occasional red blood cell in the centrifuged sediment. Stool: guaiac, 1 plus. Blood chemistry: non-protein nitrogen, 17 mg. per cent; total protein, 5.9 Gm. per cent; albumin, 2.1; globulin, 3.8 Gm. per cent; cephalin-cholesterol flocculation, 2 plus; thymol turbidity, 26 units; prothrombin time, 27 per cent of normal; icterus index, 31 units; van den Bergh test, sodium bilirubinate, 2.5 mg. per cent; bilirubinglobin, 3.4 mg. per cent; total bilirubin, 5.9 mg. per cent. Blood culture: negative.

The patient was treated symptomatically. The day after admission the abscess on the

left thigh was opened; approximately 1 pint of purulent material was withdrawn and a drain was inserted. That night she developed spontaneous ecchymoses in the right deltoid region. Following drainage of the thigh abscess, however, she felt better and her temperature decreased somewhat. Spontaneous skin hemorrhages continued to occur. On the day before death her red cell count was 2,730,000, with 9.1 Gm. of hemoglobin. Her white cell count had risen to 15,050 and the differential count showed a left shift; the white cells were described as showing marked toxic granulation. The blood platelet count was 51,000. The patient received 500 cc. of fresh whole blood without reaction. On the final day of life, November 5, 1948, she complained of nausea and vomited early in the morning. The vomitus contained no blood. She was given a small amount of dilaudid for her restlessness. That afternoon she was found dead in bed. Tarry, fecal material issued from the rectum.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents a number of interesting problems, and we shall not have time to discuss them all. We shall, however, attempt to cover the most interesting and important points. This young woman had apparently enjoyed good health until the time she developed jaundice which was essentially asymptomatic. She was admitted as a patient on the surgical service where a diagnosis of acute catarrhal jaundice was made. Dr. Wade, would you comment on that diagnosis: On the basis of the data at hand what diagnosis would you make?

DR. LEO J. WADE: The term "acute catarrhal jaundice" is misleading and should be discarded. We would rather use "acute infectious hepatitis" to characterize this disease entity.

DR. W. BARRY WOOD, JR.: I agree with Dr. Wade's comment regarding the term acute catarrhal jaundice. Probably the illness which used to be called acute catarrhal

jaundice was the same as that which we now call acute infectious hepatitis.

DR. GUSTAVE J. DAMMIN: I believe that leptospirosis of the liver has also been called acute infectious hepatitis. In my opinion we should be more definite—since this disease is viral in origin and epidemic in character, it should be called “epidemic viral hepatitis.” In that way we likewise differentiate between it and homologous serum jaundice, a disease which is also viral in origin but which is transmitted in a different way.

DR. ALEXANDER: Viral epidemic hepatitis and homologous serum jaundice are similar in their clinical pictures although there are certain significant differences in the two. The question as to whether they are one disease or two diseases has now been clarified and I shall ask Dr. Harford to compare these two syndromes.

DR. CARL G. HARFORD: The two viruses are closely related but there are, as you have pointed out, Dr. Alexander, significant differences. For example, the virus of homologous serum jaundice, or serum hepatitis as it is sometimes called, is not found in feces and it is not transmissible by ingestion of fecal filtrates. In contrast, viral epidemic hepatitis may be transmitted by ingestion of fecal filtrates and the virus often may be recovered from the stools of patients with the disease. Furthermore, the incubation period in homologous serum jaundice is much longer than is the case with viral epidemic hepatitis and the virus of the former may be detected in the blood very early in the incubation period; I believe, in one instance at least, the virus was isolated eighty-seven days before icterus developed. Patients who have recovered from one of the two forms of jaundice are said to be susceptible to the other. It has been extremely difficult to elucidate all the desired facts for these diseases can be produced only in human volunteers.

DR. ALEXANDER: Do you believe the causative agents are variants of the same virus or do you believe they are different viruses?

DR. HARFORD: It is my opinion that the two are very closely related, probably in much the same way as different strains of the influenza virus are related or as St. Louis encephalitis is related to equine encephalitis. It is not uncommon for two related viruses to cause very similar disease pictures in humans or animals.

DR. ALEXANDER: We should now return to the case under discussion. It will be recalled that following discharge from the hospital the patient's jaundice did not regress and two months later she returned for the second admission. Following study of the liver function, an exploratory laparotomy was performed. I should like to ask Dr. Moore whether or not liver function tests may be used in an attempt to differentiate between jaundice due to extrahepatic biliary obstruction and jaundice primarily due to hepatocellular damage.

DR. CARL V. MOORE: In a very high percentage of cases one should be able to differentiate between hepatogenous jaundice and extrahepatic obstructive jaundice on the basis of liver function studies. In this patient data are available to permit such differentiation and a diagnosis of hepatogenous jaundice can be made with reasonable certainty. For example, the cephalin-cholesterol flocculation was 3 plus on one occasion and then 1 plus. Thymol turbidity was elevated and it is particularly significant that the second determination was probably higher than the first since the first determination was recorded to be greater than 24 units. The alkaline phosphatase was only 4 Bodansky units and if one takes that finding with the others he can, with reasonable assurance, assume that there was no extrahepatic obstruction. The results of the liver function studies justified exploratory laparotomy for the purpose of obtaining a liver biopsy but such laboratory data as these do not constitute an indication for exploration of the common bile duct. I should like to call attention to the statement in the protocol, “she did not restrict her activities.” I believe it is well to point out here that there is very

little in the way of specific therapy in the treatment of hepatitis. One of the considerations in the management of such patients, which is now generally accepted, is that their activity should be greatly restricted during the active phase of the disease. It has been shown rather clearly that a return to activity before recovery occurs definitely exerts an untoward effect.

DR. ALEXANDER: I should like to ask Dr. Robert Moore to describe the histologic findings at the time of liver biopsy.

DR. ROBERT A. MOORE: The hepatic tissue was divided into lobules but the lobulation was irregular; in a number of areas connective tissue divided a given lobule. The connective tissue was loose and heavily infiltrated with lymphocytes and mononuclear cells. Some of the hepatic cells were binucleated; this observation may be interpreted as indicating that the liver had suffered injury and active regeneration of hepatic cells was taking place. The cytoplasm of the cells was reticulated as one would expect if there were reasonable storage of glycogen. All in all, there was a definite increase in fibrous tissue and marked lymphocytic infiltration. If one considers the findings objectively, he must conclude that the liver had been subject to injury over a moderately lengthy period of time, this statement being based on the definite increase in fibrous tissue. Further, it seems that the noxious stimulus was still active, as evidenced by the heavy infiltration of cells within the fibrous tissue and by the fact that the liver cells were actively dividing.

DR. ALEXANDER: Following operation the patient made an uneventful recovery and continued to feel remarkably well. Her third admission was for re-evaluation.

DR. WOOD: Had she continued to be fully active following operation?

DR. RALPH V. GIESELMAN: Yes, she had.

DR. ALEXANDER: She continued to have a good appetite and physical examination was essentially unchanged. Her laboratory findings, however, were perhaps somewhat more abnormal. The bilirubin had risen

and the cephalin-cholesterol flocculation was now 4 plus. Likewise, the thymol turbidity was increased and it reasonably would be concluded that the disease was progressing. By the time of her fourth admission, one month later, she had become quite ill. Bleeding from the gums and into the skin had occurred and in addition marked dependent edema and ascites developed. Dr. Smith, would you tell us why, in your opinion, this patient developed edema and ascites?

DR. JOHN R. SMITH: The sudden appearance of edema in a patient such as this one raises the question first of all as to whether marked portal hypertension had developed. The accumulation of ascitic fluid, perhaps largely at first on the basis of increased hydrostatic pressure within the abdomen, may lead to compression of the vena cava, elevation of the venous pressure in the legs and edema. I am not sure that the hypoalbuminemia was severe enough to explain the edema *per se*.

DR. C. V. MOORE: If one calculates the osmotic pressure on the basis of the plasma protein figures given, he finds that the results indeed are low enough to explain the occurrence of edema.

DR. ALEXANDER: The patient subsequently had episodes which suggested thromboses in the veins and in the arteries. You will remember that at the age of twenty-one following a respiratory infection she had remained in bed for five weeks because of swelling in her legs and that subsequently she had varicose veins and recurrent leg swelling. Do you believe that she had severe thrombophlebitis at that time?

DR. SMITH: I believe that she may well have had severe phlebothrombosis and as a result chronic severe obstruction developed.

DR. ALEXANDER: During her stay in the hospital the patient received intensive treatment including parenteral vitamin B complex, serum albumin, transfusions and crude liver extracts. Intrahepatol was also given. Dr. Moore, would you comment on the latter substance?

DR. C. V. MOORE: My experience with intrahepatol has been limited. We have been discouraged, however, by the severe febrile reactions in patients to whom it has been given. Dr. Shank and Dr. Charles Hoagland at the Rockefeller Institute used intrapheptol extensively; may we have Dr. Shank discuss this agent?

DR. ROBERT E. SHANK: At the Hospital of the Rockefeller Institute we treated a group of forty patients with cirrhosis with crude liver extract prepared in the laboratory there. It differed only from the crude commercial preparations in that the pH of extraction was higher and pyrogenic substances were removed by treatment with permutit. Large quantities were administered intravenously and the patients were followed for periods of from two to four years. The survival rate after two years, which was about 70 per cent, was substantially greater than that reported by Patek and others using dietary therapy alone. Intrahepatol is a commercial modification of the original preparation. The pharmaceutical house which prepares it has attempted to concentrate the product. In a limited experience it was our impression that reactions occurred somewhat more frequently than with the original extract.

DR. ALEXANDER: At the time of the patient's final admission her liver function tests seemed to have improved, particularly when compared with the results of her studies on previous admissions. Would you comment on that point, Dr. Dammin?

DR. DAMMIN: There are several instances in which cirrhosis has progressed to an extreme degree, concomitantly with the return of thymol turbidity and cephalin-cholesterol flocculation values to normal. In this case the very prolonged prothrombin time and the failure of response to vitamin K suggest severe hepatic damage. It should be pointed out that no one knows exactly what the thymol turbidity and cephalin-cholesterol flocculation tests measure. There is some evidence that they represent abnormality in the nature of protein components and that they

may not actually reflect what is happening in the liver cells *per se*.

DR. ALEXANDER: Let us attempt to establish the etiology in this case if possible. Is this history entirely compatible with epidemic viral hepatitis?

DR. SHANK: Yes, I think it is. It is not unusual for patients with this disease to have prolonged periods of low grade fever. More frequently this febrile period is brief. Most patients recover from epidemic hepatitis in a period of from four to nine weeks. The acute course, however, may be prolonged in some individuals and hepatic function may return to normal only after periods of months. In another group of cases intermittent, acute episodes occur with ultimate recovery. Finally, a small but important number of patients following an attack of epidemic hepatitis are left with residual hepatic dysfunction. Some of this group develop cirrhosis. It is impossible at this time to state the frequency with which cirrhosis occurs. Our experience has not been of sufficient duration to afford us adequate data but among some 400 patients studied at the Hospital of the Rockefeller Institute there were two deaths. One of these patients died in the acute phase of the disease. A number of other patients now have evidence of persistent hepatic dysfunction. Other investigators have found a higher incidence of cirrhosis, but there are some groups in which the incidence is indeed very low.

DR. ALEXANDER: The biopsy specimen which Dr. Moore showed us was obtained three months after the onset of jaundice and as you will recall showed marked fibrosis. Do you believe that this entire process may have occurred within these three months?

DR. SHANK: Yes, I do.

DR. ALEXANDER: Could this disease have been so-called toxic cirrhosis such as is seen in metal intoxication?

DR. SHANK: The course of that type of liver damage is usually quite acute, leading to death rather rapidly or at least to a prolonged severe course.

DR. VIRGIL C. SCOTT: When this patient first became ill, the liver was not the only organ affected. I would like to have Dr. Shank discuss this point.

DR. SHANK: It is true that the major pathologic findings in viral hepatitis are in the liver but many patients have splenomegaly and frequently there is gastrointestinal involvement such as gastroduodenitis. Often widespread lymphoid hyperplasia is demonstrable. I think it is well to consider this disease as a generalized infection with most prominent manifestations in the liver.

DR. ALEXANDER: Do you believe that the pathologists will be able to establish the diagnosis of viral epidemic hepatitis without qualification?

DR. SHANK: The morphologic findings demonstrable at autopsy in cirrhosis which follows epidemic viral hepatitis are variable and do not permit differentiation from other types of cirrhosis.

DR. SMITH: How frequently is infectious hepatitis followed by carcinoma of the liver?

DR. R. A. MOORE: I believe Dr. Shank's statement in regard to the fact that none of these patients has been followed for a sufficient time to know the ultimate effects applies to your question, too, Dr. Smith. So far as I know there are no specific studies on that point.

DR. ALEXANDER: I believe then that we are all agreed that this patient had epidemic viral hepatitis with progressive hepatic damage leading to cirrhosis and ultimately to death.

DR. WOOD: I would like to return for a moment to the question of terminology for I believe that this case illustrates very pointedly the need for discarding the term "catarrhal jaundice." Catarrhal jaundice was always thought to be an essentially benign disease which physicians tended to treat lightly. During the past war it was learned that infectious hepatitis was indeed a serious disease and this patient's course illustrates how very serious a form the disease may take. As Dr. Carl Moore has brought out so clearly this patient was treated actually as if she had "catarrhal

jaundice" whereas had she been treated as a patient with infectious hepatitis according to the regimen outlined by the Army physicians—that is prolonged bed rest until all evidence of hepatic disease had abated—she might well have avoided this fatal outcome.

Clinical Diagnosis: Viral epidemic hepatitis (acute infectious hepatitis), cirrhosis of the liver.

PATHOLOGIC DISCUSSION

DR. ANTONIO VILLASANA: External examination revealed light yellow discoloration of the sclerae. Over the right deltoid region, the right thigh and left ankle there were extensive areas of ecchymosis; the area over the thigh was covered with a number of blebs which contained sanguineous fluid. On the medial aspect of the left thigh and left ankle there were several ulcers and several pigmented scars; distinct pitting edema of the lower extremities was noted. The skeletal muscles, subcutaneous tissues and all the viscera were pale, somewhat dry and opaque. The heart, which weighed 400 Gm., was enlarged and flabby but exhibited no lesion other than fat infiltration of the myocardium.

There were 1,200 cc. of clear amber fluid in the peritoneal cavity. The liver, which was brownish-yellow in color, weighed 1,150 Gm. and was firm and rubbery in consistency. The left lobe of the liver was particularly small. The capsule was thickened and the surface was coarsely nodular; the size of the nodules varied from 0.5 to 4 cm. in diameter. Cut section revealed a striking difference between the right and the left lobes. The parenchyma in the left lobe was extensively replaced by edematous, translucent, yellowish-gray fibrous tissue. In the right lobe there were both small and large bulging nodules separated by the same yellowish-gray, translucent connective tissue. The spleen was enlarged to a weight of 400 Gm. It was soft and dark red with several areas of hemorrhage in the parenchyma. The stomach, which was dilated,

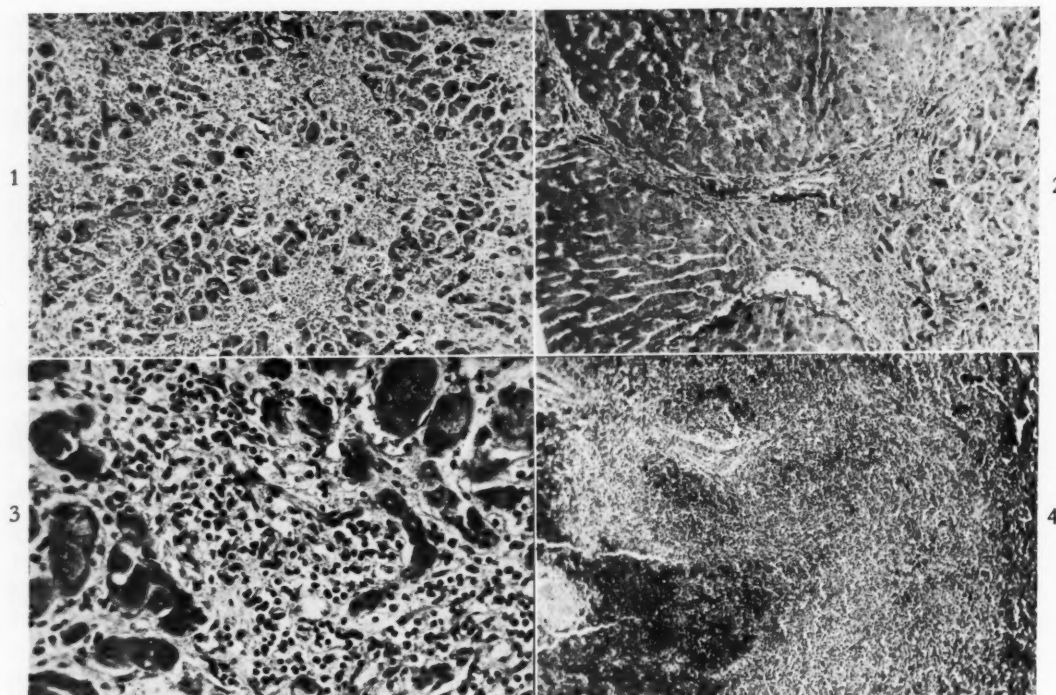


FIG. 1. A section of the left lobe of the liver composed of broad bands of connective tissue and distorted hepatic cells in small groups.

FIG. 2. Right lobe of the liver with increased periportal tissue and lobules without central veins.

FIG. 3. Details of the distorted hepatic cells with regenerative changes and cellular infiltration of the portal space.

FIG. 4. Spleen with prominent sinusoids and parenchymal hemorrhage of chronic passive congestion.

contained about 500 cc. of dark turbid fluid with food remnants and granular sediment. The gastric mucosa was smooth with few rugae and a number of petechiae. In the lumen of the large intestine there were approximately 1,000 cc. of fresh and altered blood. The mucosa was edematous, but no bleeding points could be demonstrated. In the endometrium there was a polypoid focus which on cut section revealed numerous cystic spaces filled with mucoid material. The lower peri-aortic lymph nodes were enlarged and succulent with a few petechiae in the parenchyma on cut section.

DR. R. A. MOORE: From the gross description it is apparent this case represents some type of cirrhosis of the liver; the existence of portal hypertension is suggested by the enlarged and congested spleen and the fluid in the peritoneal cavity. Presumably the terminal event can be associated with the finding of large amounts of blood in the large intestine although attempts to demonstrate a bleeding point were unsuccessful.

The first illustration (Fig. 1) was taken from the left lobe of the liver. There is diffuse fibrosis about small islands and groups of hepatic cells which show extreme multinucleation; occasionally there are actually large confluent masses of hepatic cytoplasm with multiple nuclei. The hepatic cells are not arranged in a lobular pattern and the connective tissue in between is moderately dense and mature but is infiltrated with lymphocytes and mononuclear cells to a slight or moderate degree. Contrast this picture with the next one (Fig. 2) which was taken from the right lobe of the liver. The reason for the difference in the gross appearance is immediately evident. Here there is definite lobulation; the appearance is not unlike that seen in a surgical biopsy specimen, except that at autopsy there was less activity, the connective tissue was more mature and the outline of the lobules of hepatic tissue was more distinct. Note that at the right side of the illustration there is irregular proliferation of tissue into a lobule.

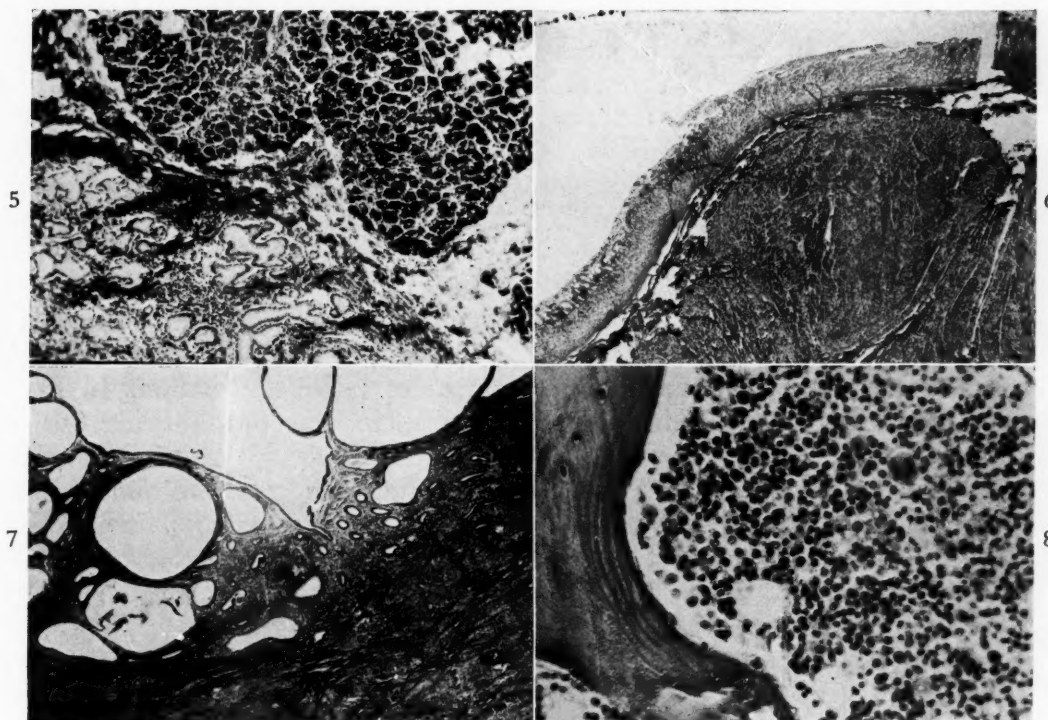


FIG. 5. Slight interstitial infiltration of lymphocytes in the pancreas.

FIG. 6. Atrophic mucosa in a section of the stomach.

FIG. 7. Endometrium with typical dilated glands of cystic hyperplasia.

FIG. 8. Moderately hyperplastic bone marrow in which there is a relative lack of the more mature erythroid forms.

The normal hepatic lobule always contains a central vein and the hepatic cells radiate in a definite cord-like pattern to the periphery. When liver regenerates, it rarely if ever regenerates in that pattern, but rather in the pattern which was noted here—the hepatic cords are not arranged in as orderly a fashion. There is a suggestion of radial arrangement but in the centers of these lobules there is no central vein. That change constitutes objective evidence that this tissue was not residual original hepatic tissue but rather regenerated hepatic tissue. The contrast in the microscopic findings in the left and right lobe of the liver represents a difference in the type and amount of regeneration. In the right lobe there had been extensive regeneration with formation of nodules while in the left lobe regeneration had not advanced to the same extent and had not taken on the lobular pattern which is so characteristic of classical cirrhosis of the liver.

Figure 3 is a section under a higher magnification from the left lobe of the liver
JULY, 1949

in which there are cells with a large amount of basophilic, globular, granular material in the cytoplasm, supposedly nucleoproteins of the cytoplasmic type associated with active regeneration; prominent nucleoli, also indicative of active regeneration, are likewise seen. Multinucleation of hepatic cells was obvious. The connective tissue was loose and infiltrated with large numbers of cells.

The next illustration (Fig. 4) is a section from the spleen. There is prominent dilatation of the sinusoids and hemorrhage into the red pulp indicative of congestion of long-standing. In a section from the pancreas (Fig. 5) there is slight interstitial fibrosis and cellular infiltration of a few lymphocytes, particularly out into the paraductal tissue. The next section (Fig. 6) is taken from the stomach and shows mucosa with the muscularis beneath it. The mucosa was definitely atrophic and thinner than normal. Atrophy involved not only the gastric mucosa but also the duodenal mucosa as well.

A section of the endometrium (Fig. 7)

shows the typical changes of cystic hyperplasia. This lesion is allegedly associated with some disturbance in estrogen metabolism; certainly a patient with as much hepatic damage as this woman might well have had sufficient disturbance in estrogen metabolism to have had endometrial stimulation.

Figure 8 is a section of the bone marrow showing diffuse hyperplasia; mature cells of the erythroid series are relatively decreased in number in comparison with less mature forms, indicating slight maturation arrest in the red cell series.

I think that pathologists have had more difficulty with cases of this type, particularly in regard to terminology, than have the clinicians; acute catarrhal jaundice, toxic cirrhosis and acute and subacute yellow atrophy perhaps all belong in the same category. I am not at all sure that enough is known to permit sharp morphologic distinction between these various types of hepatic disease, but the criteria of distinction which are in current use may be presented, and they apparently rest upon a reasonably firm foundation.

First, what type of cirrhosis was present in this case—was it Laennec's portal cirrhosis or some other form? Fifteen or twenty-five years ago there appeared in the pathologic literature descriptions of the type of cirrhosis which is called toxic cirrhosis—or from a descriptive standpoint, multilobular cirrhosis of the liver—in order to distinguish it from simple lobular cirrhosis of the Laennec type. That idea developed because of cases similar to the present one in which there were nodules throughout cut sections of the liver separated by variable amounts of connective tissue. In almost every instance, however, there was some focus in which lobulation was absent. To explain the origin of such a lesion it was logical to postulate that the liver was exposed to an extensive insult of very short duration which destroyed large areas to such a degree that regeneration had not, or could not, occur. In other regions the damage presumably was less severe and

regeneration occurred with resultant formation of nodules varying in size. Such was the accepted concept in regard to the pathogenesis of toxic cirrhosis.

During the last century acute yellow atrophy and subacute yellow atrophy were also described, the former being those cases which exhibited a fulminating course and massive destruction of tissue and the latter diagnosis being assigned to those cases which were less severe in their course and in the extent of tissue destruction. In the acute cases there was outright necrosis of the hepatic cells without proliferation of fibrous tissue and with only a minimal amount of cellular infiltration. In patients who survived for a sufficient period of time fibrous tissue proliferated, regeneration of liver cells ensued and the pathologic picture of subacute yellow atrophy developed.

In the course of time those two major concepts, namely, toxic cirrhosis and acute or subacute yellow atrophy, were combined to some extent, in that acute yellow atrophy in a few instances and toxic cirrhosis in some instances (but neither in every instance) were observed to follow the ingestion of some noxious substance. Cinchophen, arsenic and many other chemical agents were found to be hepatotoxic. It was inferred that single doses of these substances injured the liver and therefore the term toxic cirrhosis of the liver was thought applicable. I think it has become apparent in recent years that although the concept of acute yellow atrophy as a disease produced by toxic agents is still tenable, most examples of acute yellow atrophy, subacute yellow atrophy and toxic or multilobular cirrhosis of the liver represent varying stages of the disease, epidemic viral hepatitis.

I think this brief recapitulation of the history of the concept of this disease from the pathologic standpoint indicates that the pathologist is not in a position to make an outright diagnosis of epidemic viral hepatitis. He can, however, state that the pathologic changes are consistent with that diagnosis if it can be supported on a clinical basis. The same comments apply, of course,

to homologous serum jaundice as to epidemic viral hepatitis.

In the case which we are discussing today the lesions found in the liver are consistent with those one would expect to find in a patient with epidemic viral hepatitis who had recovered to the extent that regeneration of the liver without restoration of the normal structural pattern had occurred. Fortunately, in most patients who have epidemic viral hepatitis recovery is complete.

A finding which interested us a great deal was atrophy of the gastric mucosa and the slight maturation arrest in the red cells series. I gave Dr. Carl Moore a note earlier in the conference and asked him if he could tell us if that finding could be correlated with a lesion which had caused severe hepatic dysfunction.

DR. C. V. MOORE: It is known that in most patients with cirrhosis or severe hepatic insufficiency normocytic or slightly macrocytic anemia frequently develops which, however, does not respond to the antipernicious anemia principle in liver. Rarely, one does see a patient who has marked hepatic damage and a megaloblastic bone marrow who responds quite specifically to liver. Whether this particular patient is in that category or not I do not know, but I would doubt it. It is conceivable that the changes observed in the bone marrow and in the gastric mucosa may be explained on the basis of an antipernicious anemia factor deficiency, but I would doubt that also. Probably the bone marrow abnormality could better be related to the infection present; in this regard it is well to note that the neutrophils were deficient in granules and there were other evidences of bone marrow depression. Atrophy of the gastric mucosa probably cannot be attributed to infection.

DR. ALEXANDER: I would like to ask why Dr. Balduin Lucké stated that cirrhosis did not seem to be a sequence of epidemic hepatitis.

DR. R. A. MOORE: It is my understanding that at the time Dr. Lucké published his paper he had not seen cases such as this one. Is that not right, Dr. Dammin?

DR. DAMMIN: Yes. He later qualified his statement somewhat and said that a single bout of hepatitis does not result in cirrhosis.

DR. R. A. MOORE: Dr. Lucké's first report was based on early observations. Cirrhosis following epidemic viral hepatitis has been observed by others many times since Lucké's original paper.

It was unfortunate that in the autopsy Virchow did in 1850 on a patient who had this very disease he demonstrated mucous plugs in the ampulla of Vater and no necrosis of the liver; otherwise the whole concept of acute catarrhal jaundice would never have developed. Dr. Cecil Watson has recently demonstrated by means of multiple biopsies of the liver that there are occasions when there may be no significant microscopic changes in that organ during the disease.

DR. DAMMIN: In this case the liver function tests revealed a progression of the disease. At the time of exploration the surgeon noted that the liver was uniformly enlarged but at autopsy the left lobe was more severely scarred than the right. It is postulated that this difference occurs because the elements that protect the hepatic parenchyma are apparently drawn from the small intestine and reach the right lobe of the liver in greater concentration than the left lobe which is consequently less protected.

Anatomic Diagnoses: Cirrhosis of the liver with predominantly peripheral fibrosis and marked reduction in parenchyma; fresh and altered blood in the gastrointestinal tract (1,000 cc.); atrophy of the gastric and duodenal mucosa; hyperplasia of the vertebral marrow; cystic hyperplasia of the endometrium.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING HELD IN NEW ORLEANS, JANUARY 28, 1949

IMMUNE RESPONSE TO H. PERTUSSIS VACCINATION. A STUDY USING THE PASSIVE INTRAPERITONEAL MOUSE PROTECTION TEST. *John P. McGovern, M.D., (introduced by Grant Taylor, M.D.), Durham, North Carolina.*

Mouse protective antibodies were assayed and compared with agglutinating antibodies following immunization with a phase I H. pertussis vaccine in a group of young infants. A total of thirty infants, three to six months of age with no history of or exposure to clinical whooping cough, were subjected to inoculation three times at two-week intervals with a phase I pertussis vaccine, each infant receiving an approximate total of 100 billion organisms. Blood samples were drawn before as well as after immunization. Sera from these blood samples were used in an attempt to protect mice passively against lethal intraperitoneal challenging doses of pertussis organisms suspended in a 4 per cent gastric hog mucin solution. Each serum was also tested for agglutinating antibodies by a rapid agglutination technic. Control groups of mice were used in each experiment.

It was found that these infants did not possess mouse protective antibodies in their serum but that these antibodies consistently develop following inoculation of the infant with sufficient phase I pertussis vaccine. It was shown also that agglutinating antibodies did not develop consistently nor did they parallel in degree the mouse protective values.

DIFFUSION OF STREPTOMYCIN INTO SEROUS CAVITIES FOLLOWING INTRAMUSCULAR INJECTION. *Patrick B. Storey, M.D. (by invitation), Walter Kurland, M.D. (by invitation), Helen Murphy, B.S. (by invitation), Sol Katz, M.D. (by invitation) and Harold L. Hirsh, M.D. (introduced by Jay A. Robinson, M.D.), Washington, D. C.*

From the Georgetown Medical and Tuberculosis Divisions, Gallinger Municipal Hospital, and Department of Medicine, Georgetown University School of Medicine.

Spinal fluid was obtained from thirty-eight patients with pulmonary tuberculosis without meningitis. All but two of the patients studied had had therapy for at least three weeks. The two patients were studied during the first two days of therapy in order to determine the rapidity with which streptomycin appeared in the spinal fluid. On dosage schedules of 1 Gm. every six hours streptomycin was not detected in the spinal fluid one or two hours after the first dose whereas assayable levels were found at twelve hours. Of the twenty patients who were receiving 2 to 4 Gm. per day in divided doses every six to twelve hours, all had spinal fluid concentrations of 0.15 to 0.6 micrograms per cc. Only 50 per cent of the patients receiving 1 Gm. per day had a level of 0.15 to 0.3 micrograms per cc. of spinal fluid. Two patients with tuberculous meningitis were treated with streptomycin intramuscularly, one of whom received 1 Gm. every twelve hours and the other 1 Gm. every six hours. In the first patient repeated specimens of spinal fluid were found to contain 0.3 micrograms per cc. Assay of specimens of spinal fluid from the second patient revealed no detectable levels at one hour, 2.5 micrograms per cc. at twelve hours and 5 micrograms per cc. at twenty-four and seventy-two hours after therapy was started.

Four patients with infectious arthritis and one with hydro-arthritis who were on streptomycin intramuscularly in doses of 1 and 3 Gm. per day were studied. Joint fluid levels obtained during therapy ranged from 2.5 to 5.0 micrograms per cc.

There were ten patients with acute tuberculous pleurisy with effusion who received doses of 1 to 2 Gm. of streptomycin per day. Maximum levels of 2.5 to 5.0 micrograms were found in the pleural fluid after several days of therapy.

Two patients with portal cirrhosis on dosage schedules of 1 to 2 Gm. of streptomycin per day showed from 2.5 to 5.0 micrograms per cc. of ascitic fluid. One patient with a tuberculous pericardial effusion on a 2 Gm. per day dosage schedule showed levels of 5 and 10 micrograms per cc. of pericardial fluid.

THERAPEUTIC VALUE OF SMALL DOSES OF STREPTOMYCIN IN TUBERCULOSIS. *Bernard Milloff, M.D. (by invitation), Sol Katz, M.D. and Harold L. Hirsh, M.D., (introduced by Hyman Zimmerman, M.D.), Washington, D. C.*

From the Georgetown Medical and Tuberculosis Divisions, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine.

A variety of tuberculous infections were treated with small doses of streptomycin. All patients received $\frac{1}{2}$ Gm. per day in one dose, except four with miliary tuberculosis who were given $\frac{1}{2}$ Gm. twice a day.

Five patients with miliary tuberculosis were treated and none survived. Four patients with bronchial tuberculosis treated for one to four months showed a definite beneficial response. Two patients with proved tuberculous pericarditis were treated. In one the response was favorable while the other developed progressive tuberculosis and died. Two patients showed clearing of the tuberculous peritonitis, however, several months after completion of therapy hematogenous tuberculosis became manifest in both. Treatment was re-instituted with no response.

Seven patients with draining sinuses showed closure of the sinuses. In two patients with tuberculous bursitis incision and drainings while under streptomycin therapy resulted in healing. In forty patients with eighty-six operations, which included thoracoplasty, lobectomy and pneumonectomy, no tuberculous spreads occurred with the use of $\frac{1}{2}$ Gm. per day in a single injection for seven days preoperatively and postoperatively.

Streptomycin in doses of $\frac{1}{2}$ Gm. per day would appear to be definitely effective in the treatment of bronchial tuberculosis and draining sinuses. It would also be recommended that this same dosage be used in the prevention of tuberculous spread in the surgery of tuberculous patients.

JULY, 1949

GROWTH ENHANCEMENT OF M. TUBERCULOSIS BY STREPTOMYCIN. *Max Michael, Jr., M.D., Martin Cummings, M.D., George Spendlove, M.D. and William B. Fackler, Jr., M.D., Atlanta, Georgia.*

From the Medical Service, Lawson VA Hospital and the Department of Medicine, Emory University School of Medicine and the Tuberculosis Evaluation Laboratory, USPHS.

The development of bacterial resistance to streptomycin is a well documented phenomenon. Of recent interest is the finding that a few strains of bacteria appear to be not only resistant to but actually dependent upon streptomycin for growth. This study is concerned with a strain of the tubercle bacillus which demonstrates enhancement of growth by streptomycin. The strain was isolated from the sputum of a patient with pulmonary tuberculosis on the ninety-sixth day of streptomycin therapy. It was the impression of the observers that the disease was actually made worse toward the end of the course of streptomycin but it is obviously difficult to draw any conclusion as to cause and effect in a disease of such clinical variability.

The organism displayed the following characteristics: When cultured in tubes containing 0, 1, 5, 10, 100 and 1,000 micrograms per ml. of streptomycin it grew luxuriantly in all tubes containing streptomycin but quite sparsely in the control tube without the antibiotic. This was observed repeatedly, both in liquid Dubos media and on solid Lowenstein media. A sample of the patient's sputum obtained three months after the termination of therapy displayed the same phenomenon.

Guinea pig experiments have suggested that the observed enhancement of growth *in vitro* also occurs *in vivo*. Animals infected with this strain and treated with streptomycin had a shorter survival time than did those which were untreated.

A FACTOR IN RABBIT POLYMORPHONUCLEAR LEUKOCYTES WHICH CAUSES A RISE IN BODY TEMPERATURE. *Paul B. Beeson, M.D., Atlanta, Georgia.*

A plausible explanation of the fevers which accompany many different kinds of disease is that some product of tissue injury affects the

function of temperature-regulating centers in the hypothalamus. The findings described here were obtained during an attempt to demonstrate such a substance. Rabbits were used as experimental animals. Various types of tissue were subjected to mechanical lysis and then tested for capacity to cause elevation of temperature in normal rabbits. The following cells or tissues have been so studied: erythrocytes, lymphocytes, macrophages, polymorphonuclear leukocytes, liver, brain, kidney, lung, spleen and muscle. Positive results were obtained only with polymorphonuclear leukocytes. These were obtained from intraperitoneal exudates produced by injection of large quantities of sterile physiologic salt solution. The cells were separated from the exudates by centrifugation, washed and then lysed by shaking with glass beads. Centrifugation of this material in a small quantity of saline yielded a clear supernatant fluid and cellular debris. The cellular debris did not provoke fever but the clear supernatant fluid was active. An extract of leukocytes obtained from the peritoneal exudate of one rabbit produced a rise of 1 to 3°F: within one hour when injected intravenously into a normal rabbit. The agent responsible for the temperature rise was not dialyzable through a collodion membrane and was inactivated by heating to 75 to 80°F. It was not precipitated at 50 per cent saturation with sodium sulfate but was precipitated at full saturation. The activity of this factor is inhibited by antipyretic drugs.

METABOLIC CHANGES ASSOCIATED WITH THE ADMINISTRATION OF SALT-POOR HUMAN SERUM ALBUMIN IN INFECTIOUS HEPATITIS.
W. Parson, M.D., H. S. Mayerson, M.D. (by invitation), W. J. Trautman, Jr., M.D. (by invitation) and R. Hutcheson, M.D. (by invitation), New Orleans, Louisiana.

From the Departments of Physiology and Medicine, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation.

Two patients suffering from infectious hepatitis were studied on a metabolic regimen for periods of thirty to thirty-five days, respectively. Large doses (75 Gm.) of salt-poor human serum albumin were administered daily during two separate six-day periods to the first patient and during one six-day period to the second patient. The latter was subsequently fed a protein

supplement during one period and the results were compared with those obtained after albumin administration. Daily nitrogen, calcium and phosphorus balances were obtained as well as frequent determinations of the plasma proteins, red cell and plasma volumes. The results indicate that administered salt-poor human serum albumin is retained almost quantitatively and can be considered as a useful source of nitrogen in situations in which marked anabolism is present.

VITAMIN B₁₂ THERAPY FOR MEGALOBlastic ANEMIA OF INFANCY. *A. Z. McPherson, M.D. and U. Jonsson, M.D. (introduced by Grant Taylor, M.D.), Durham, North Carolina.*

A severe anemia with megaloblastic blood formation in the marrow occasionally develops in infancy in association with infection and/or dietary inadequacy. The anemia responds specifically to liver extract or to pteroylglutamic acid.

Two infants with megaloblastic anemia were treated with vitamin B₁₂ with favorable results. An eleven months old colored infant had been fed only breast milk. Development was retarded. She finally became weak, irritable and acutely ill. On admission the hemoglobin was 3.2 Gm./100 cc., red blood cells 1,100,000, white blood cells 20,000, hematocrit 10 per cent, mean corpuscular volume 92 cu. micra., reticulocytes 7.4 per cent and platelets 24,000 per c.u. mm. Immature granulocytes and nucleated red blood cells were present in the circulating blood. The bone marrow showed megaloblastic cell development. A single dose of 0.002 mg. of vitamin B₁₂ was injected intramuscularly. On the seventh day a reticulocyte peak of 69.1 per cent was reached and the blood values had more than doubled. On the fourteenth day the hemoglobin was 7.8 Gm., red blood cells 2,800,000, white blood cells 13,350, hematocrit 30 per cent, mean corpuscular value 104 cu. micra. and reticulocytes 13.5 per cent. The platelets were normal in number and immature granulocytes were no longer present in the circulating blood although a few nucleated red blood cells still remained. The bone marrow was normoblastic.

A second infant, a seven months old white male, had eaten poorly for four months despite an adequate diet. Anemia was discovered before

admission and blood transfusions were given. He remained weak, ate poorly and vomited often. The hemoglobin was 10.9 Gm./100 cc., red blood cells 3,100,000, white blood cells 5,500, hematocrit 29.5 per cent, mean corpuscular value 93 cu. micra. and reticulocytes 1.3 per cent. Bone marrow examination showed megalo-blastic cell development. Vitamin B₁₂ (0.002 mg.) was injected intramuscularly. The blood values continued to fall for six days. Vitamin B₁₂ (0.005 mg.) was then injected and two days later an unsustained reticulocytosis of 31.7 per cent occurred. With a daily dose of 0.002 mg. of vitamin B₁₂, there was a sustained reticulo-cytosis and rapid gain in blood values.

TREATMENT OF ACUTE LEUKEMIA WITH AMINOPTERIN. *Paul Maness, M.D., O. C. Hansen-Pruss, M.D., A. Z. McPherson, M.D. and Leland D. Stoddard, M.D. (introduced by Grant Taylor), Durham, North Carolina.*

Nine patients with acute leukemia, seven children ranging in age from thirteen months to fourteen years and two adults twenty-five and forty-five years old, were treated with aminopter-in. In seven patients the leukemia was myeloblastic and in two it was lymphoblastic. The total dose of the drug per patient varied from 3.5 to 20 mg. Stomatitis developed in four patients. Leukocytosis in five patients decreased but there was no improvement in the hemoglobin or red cell values. Serial bone marrow examinations showed some increase in cell maturity in four cases during aminopterin therapy. A temporary remission lasting three weeks or longer occurred twice. Four patients died in the hospital after being treated from three days to five weeks. Some evidence of hematologic improvement attributable to the drug was seen in three of these patients. Three patients continue to take the drug. One child with lymphoblastic leukemia showed no observable effect from the drug and in the other there was a fall in the white cell count and symptomatic improvement after taking 20 mg. in one month.

Autopsy study in four cases showed focal areas of hemorrhage and necrosis in the bone marrow as the outstanding finding.

While aminopterin has a demonstrable hem-atologic effect in some patients with leukemia,

and may even produce a temporary remission, the net clinical benefit does not appear to be great enough to justify its use except in experi-mental therapy.

CHEMOTHERAPEUTIC ACTIVITY OF DERIVA-TIVES OF PTEROYL GLUTAMIC ACID AGAINST TRANSMITTED LEUKEMIA IN MICE. *J. H. Burchenal, M.D., J. R. Burchenal, M.D. and E. Robinson, M.D., New York, New York.*

From the Section on Mouse Leukemia of the Division of Experimental Chemotherapy, the Sloan-Kettering Institute for Cancer Research.

Because of the promising results reported by Farber and others from the use of 4-amino-pteroyl glutamic acid in the treatment of acute leukemia, it was believed that compounds structurally related to pteroyl glutamic acid should be screened against transmitted mouse leukemia. Leukemia Ak 4, an acute lymphoid strain in the Akm stock of mice, was used in these experiments. Most of the ninety derivatives tested to date have shown no real chemo-therapeutic activity, but the four following compounds significantly prolonged the survival time of the treated animals: 4-amino-N¹⁰-methyl-pteroyl glutamic acid; 2, 6-diamino-purine; 4-amino-pteroyl aspartic acid and 4-amino-pteroyl glutamic acid.

Repeated tests of these compounds have demonstrated that 4-amino-N¹⁰-methyl-PGA and 2,6-diaminopurine consistently prolonged by from 50 to 100 per cent the survival time of mice injected with this strain of leukemia. Less work has been done to date on 4-amino-pteroyl aspartic acid but these experiments as well as others against less acute leukemias indicate that this compound has a chemotherapeutic activity approximately equal to the two just mentioned. 4-amino-pteroyl glutamic acid is the most toxic of the derivatives so far tested, but it does not show as great an effect on transmitted mouse leukemia as the other three.

It is interesting to note that these four com-pounds have analogous structures. The simi-larity lies in the substitution by amino groups in the 2 and 4 positions of the pyrimidine ring. All have also been shown to act in varying degrees as antagonists of pteroyl glutamic acid in the growth requirements of *Lactobacillus casei*.

EFFECTS OF 4-AMINO-PTEROYL GLUTAMIC ACID AND RELATED COMPOUNDS ON NEOPLASTIC DISEASE. *J. H. Burchenal, M.D., D. A. Karnofsky, M.D., W. P. L. Myers, M.D., C. M. Southam, M.D., L. F. Craver, M.D. and C. P. Rhoads, M.D., New York, New York.*

From the Section on Mouse Leukemia of the Division of Experimental Chemotherapy, the Sloan-Kettering Institute for Cancer Research.

A total of thirty-eight patients with leukemias and various forms of neoplastic disease have been treated with 4-amino-pteroyl glutamic acid at Memorial Hospital since March, 1948. Doses have varied from 1 mg. per day in children to a top dose of 4.7 mg. a day over an eight-day period for one adult. Toxic symptoms were frequent in our series. Of the thirty-one patients who received at least 0.2 mg./Kg. and were observed for at least forty-eight hours after the start of therapy twenty-six developed stomatitis, nine diarrhea, nine loss of hair and five various types of rash.

Thirteen patients with acute leukemias, seven children and six adults, were treated. Of these nine died without any significant benefit and two had temporary partial remissions lasting about five weeks and then they died despite further therapy, 107 and 185 days, respectively, after the start of treatment. Two patients are surviving with almost complete clinical and hematologic remissions. In one of these patients there have been three separate remissions following re-administration of the drug.

Nine patients with chronic myelocytic leukemia were treated. Two of them were terminal and died before receiving adequate amounts of the drug for evaluation. Of the remaining seven a fall in white blood cells occurred in all, there was improvement in the differential count in six, a rise in hemoglobin in two, a decrease in the spleen size in five and subjective improvement in six. Three patients with chronic lymphocytic leukemia were treated with no benefit and a high incidence of toxic manifestations. Five patients with Hodgkin's disease, four lymphosarcomas in adults, two carcinomas of the lung and one carcinoma of the bladder and one mycosis fungoides, showed little or no response to therapy even when the dosage was pushed to toxic levels.

BONE MARROW STUDIES IN PATIENTS TREATED WITH 4 AMINO-PTEROYLGLUTAMIC ACID, 4 AMINO N¹⁰ METHYL PTEROYLGLUTAMIC ACID AND 4 AMINO-PTEROYL-ASPARTIC ACID. *J. B. Thiersch, M.D. (introduced by J. H. Burchenal, M.D.), New York, New York.*

Serial bone marrow examinations were conducted on twenty-one patients with tumors and leukemia who were treated with antifolic compounds. The effect of these compounds on the myeloid and erythroid series was studied and no qualitative distinction between the action of the different agents was found. The myeloid elements were markedly decreased; the eosinophiles being least affected. Giant metamyelocytes and hypersegmented polymorphonuclears appeared in abnormal numbers. The erythroid series, while decreased *in toto*, appeared to be relatively prominent compared to the myeloid series. Pathologic nuclear remnants often combined with coarse basophile stippling were found in giant erythrocytes. The orthochromatic normoblasts were decreased in numbers and sometimes absent. Basophile normoblasts and erythroblasts increased and finally atypical but definite basophile megaloblasts appeared, reaching a maximum of 52 per cent of all nucleated erythroid elements. Platelets and megacaryocytes were less affected.

An erythromegaloblastosis was produced in patients with lymphosarcoma and chronic lymphatic leukemia. This was reversed in eight days with folic acid in one case but did not remit spontaneously in twenty-nine days in one other case. No effect on the lymphoid series was observed in these patients.

Two cases of acute leukemia responded with megaloblastic changes in the erythroid series and further decrease of the mature myeloid elements. Patients with chronic myeloid leukemia gave only a moderate decrease of total cellularity and changes in the erythroid series as just described.

Two patients with lymphosarcoma with bone marrow involvement and two patients with acute leukemia showed a decrease in abnormal cells and a reversion toward normal composition.

EXTRACELLULAR WATER CONTENT OF THE HEART IN DOGS SUBJECTED TO HEMORRHAGIC SHOCK MEASURED WITH THE RADIOACTIVE ISOTOPE OF SODIUM. *Ned D.*

Rodes, M.D., Janet M. Lemley, M.D., Alice B. Dale, M.D., Sam E. Stephenson, Jr., M.D., Herbert L. Glass, M.D. and George R. Meneely, M.D., Nashville, Tennessee.

From the Departments of Biochemistry, Medicine and Surgery of Vanderbilt University School of Medicine and the Research Laboratory of Thayer Veterans Administration Hospital, Nashville, Tennessee.

The method of Manery and Bale was employed to measure the extracellular water of the myocardium in three groups of dogs. The first group was subjected to severe hemorrhagic hypotension to produce irreversible shock by the technic of Wiggers. The second group represented positive controls in that they were treated in the same manner as the shock dogs but were not bled. The third group, which served as negative controls, were given large and rapidly administered intravenous infusions of saline.

The positive control dogs showed an extracellular water content in the myocardium of 23.5 per cent of the wet weight of tissue. This is in quite close accord with the data of Manery and Bale. The negative control dogs developed an edema of the myocardium obvious on gross and microscopic examination. The extracellular water in these hearts was 46.2 per cent of the wet weight of the tissue. This is significantly and convincingly different from the positive controls. Thus the method is adequate to detect edema when it is present.

The extracellular water in the myocardium of the dogs subjected to Wiggers' hemorrhagic hypotension procedure was 24.7 per cent of the wet weight of tissue. There is, therefore, no edema of the heart in dogs subjected to this form of irreversible shock.

DETERMINATION OF PLASMA VOLUME USING HUMAN SERUM ALBUMIN TAGGED WITH RADIOACTIVE IODINE 131. *Robert Nieset, M.D. (by invitation), Blanche Porter, M.D. (by invitation), and Kenneth R. Crispell, M.D. (by invitation) (introduced by William Parson, M.D.), New Orleans, Louisiana.*

From the Biophysics Laboratory, Tulane University.

Human serum albumin was chosen as the tracer vehicle since it was desirable to develop a method applicable to humans. The tracer

chosen was I 131 since it is known to combine chemically with the amino acid, tyrosine. Human serum albumin contains approximately 4½ per cent of tyrosine. The radioactive iodine I 131, as obtained from Isotopes Division of Atomic Energy Commission, is present as an iodide. To facilitate the tagging of albumin the iodine must be available in a free state. The iodine is then combined with the albumin in an alkaline solution. The iodo-albumin mixture is dialyzed to remove all inorganic iodide compounds.

Preliminary observations were carried out on dogs. This method compares favorably with the plasma dye method in determining the plasma volume. A disadvantage of the plasma dye method is the difficulty encountered in repeated frequent determinations on the same subject. The iodo-albumin method is not subject to such limitations provided the tolerance dose of radiation is not exceeded.

Preliminary studies seem to indicate that the iodo-albumin method is applicable to human subjects. The determination of plasma volume in four patients gave values which agreed within 10 to 15 per cent with those obtained using the plasma dye method.

REGRESSION OF A RADIOACTIVE MERCURIAL DIURETIC FROM THE PLASMA OF MAN. *C. T. Ray, M.D., S. A. Threefoot, M.D., G. E. Burch, M.D., J. A. Cronvich, M.D. (by invitation), J. P. Milnor, M.D., P. B. Reaser, M.D., W. J. Overman, M.D. and W. H. Gordon, M.D., New Orleans, Louisiana.*

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital and the Department of Medicine and School of Electrical Engineering.

During the study of the mechanism of chronic congestive heart failure and other edematous states investigations were carried out with the use of radioactive mercury incorporated into a mercurial diuretic (mercuhydrin) in order to observe the concentration-time course of the isotope in the plasma of man after intravenous injection. Fifteen subjects were studied. Labeled mercurial diuretic (2 cc.) were injected into the antecubital vein of one arm of the subjects, and blood samples were drawn at close intervals from the antecubital vein of the contralateral side. The serum concentration regression curves

observed in all subjects were similar. The curves were analyzed graphically into three exponential rates of regression.

The regression rates contributing to the concentration-time course of radioactive mercury in the plasma of man are not simple phenomena; rather they are probably the expression of many simultaneously occurring physicochemical processes. The most rapid regression rate is brought about largely by mechanical mixing of the tracer in the plasma along with some extremely rapidly occurring biologic events. The second regression rate probably expresses the filling of the potential mercury spaces and the activation of "potential turnover patterns" for mercury, including diffusion and chemical reactions, which did not actually exist until a relatively large quantity (78 mg.) of the element was administered. The third regression rate is most likely primarily a reflection of the elimination of the mercury from the body, principally urinary.

This analysis of the regression of mercury from the plasma of man is undoubtedly an oversimplification of multiple complex phenomena but it serves as a basis for an understanding of other data dependent upon the concentration of mercury in the plasma.

CLINICAL USE OF THE NEW MONOTHIOL MERCURIAL DIURETIC—THIOMERIN. *A. Ruskin, M.D., J. E. Johnson, M.D. and W. N. Roddy, M.D., Galveston, Texas.*

In experiments on the isolated rabbit heart we noted the cardiotoxic and cardiolethal dosages of thiomerin (Campbell) to be approximately twenty times those of meralluride (mercuhydrin), the diuretic in present use.

The subcutaneous administration in patients with edema of various origins, 2 cc. doses, of equal mercury content (80 mg.) in daily rotation with 2 cc. of mercuhydrin produced the following results: In twenty-four instances the twenty-four-hour weight loss was identical following either diuretic; in sixty-two patients thiomerin produced up to three times as great a weight loss; in twelve the weight loss was from four to nine times as great with thiomerin as with mercuhydrin. Mercuhydrin was followed by a greater weight loss up to three times that following thiomerin in fifty instances; in ten the weight loss was four to eight times greater.

These results indicate the near-equivalence

of diuretic effects following doses of mercuhydrin and thiomerin of equal mercury content. The maximum weight loss for either drug was 9 pounds, the maximum excess of output over the intake 7 L. Reactions following an earlier lot of thiomerin were moderate in the form of inflammatory nodules at the site of injection; only mild infrequent soreness resulted from the newer lots of the drug. Thiomerin resulted in no toxic effects on the kidneys or the electrocardiogram. It was effective and harmless when mercuhydrin produced reactions.

VARIATIONS IN THE EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM. *Robert P. Grant, M.D. and E. Harvey Estes, M.D., Atlanta, Georgia.*

From the Departments of Physiology and Medicine, Emory University School of Medicine.

The effect of digitalis on the ECG has been recognized as one which tends to reduce the ventricular gradient to zero. In effect this means that the T wave comes to have an opposite direction but equal magnitude to the QRS. The development of methods for studying instantaneous vector components of ECG deflections and determining magnitude and direction of electrical forces of the QRS and T in space have made study of some of the properties of this phenomenon possible.

Descriptively it can be said that the T vector on digitalization gradually shrinks without changing direction and the potentials of repolarization become evident in the S-T segment. This is manifest as an S-T vector at 180° from the QRS vector. Thus by vector methods the detection of abnormal T waves (an abnormality in direction of the gradient) is often possible in the presence of digitalis ST and T effect.

The undigitalized subject on passive breath holding shows a decrease in size of the T vector but the QRS-T angle remains relatively constant. However, a partially digitalized subject showing only a slight decrease in magnitude of the T vector with no discernible ST component develops the pattern of complete digitalization—that is the resultant ST-T vector at 180° from the QRS—with this maneuver. A continuous positive pressure breathing apparatus was constructed to study this phenomenon more closely. It was found that the development of digitalis effects in the partially digitalized

subject was related to changes in intrapulmonary pressure rather than changes in arterial oxygen saturation. Other procedures which alter hemodynamics were studied in relation to the changes they produced in the effect of digitalis on the ECG.

It is evident that digitalis sensitizes the myocardial membrane to quite delicate variations in intrapulmonary pressure. Whether this is due to an alteration in the gradient of pressure across the myocardium or to other mechanisms has not yet been established. The study suggests that hemodynamic and respiratory factors such as dyspnea will play a part in the degree of digitalis effect seen in the ECG.

STUDIES ON THE EFFECTS OF DIGITOXIN ON THE COAGULATION MECHANISM. *William C. Levin, M.D. and A. Ruskin, M.D., Galveston, Texas.*

From the Department of Internal Medicine and the Hematology Research Laboratory, the University of Texas Medical School.

Heparin tolerance studies were performed on eleven patients all of whom had no evidence of cardiac decompensation or thrombo-embolic disease. These studies were made before and after the patients had received a full digitalizing dose (1.6 mg.) of digitoxin. The tolerance studies were done as described by de Takats, and by a modified method, using the Lee and White coagulation time technic. The heparin tolerance curves displayed no significant changes following digitoxin when the capillary tube technic was used. Seven of the same eleven patients showed no significant changes in heparin tolerance after digitoxin when the Lee and White method was used. Two showed decreased tolerance and two showed increased tolerance to heparin after digitoxin, using this same technic.

The problem was studied further by performing prothrombin times on nine similar patients before and after administration of digitoxin. There was no significant change in the prothrombin time. These subjects were then given dicumarol in doses of 300 mg., 200 mg and 100 mg. on three successive days while on a maintenance dose of digitoxin (0.2 mg./day). In all instances the response to dicumarol was considered normal.

Three other patients whose prothrombin activity was kept between 10 per cent and 30

per cent of normal by the administration of the necessary doses of dicumarol were given digitalizing doses of digitoxin. There was no rise of prothrombin activity above the aforementioned levels following digitoxin.

The impression has been gained that these data do not support the thesis that digitalis promotes coagulation of the blood.

CRITICAL APPRAISAL OF ANTICOAGULANT THERAPY WITH HEPARIN AND DICUMAROL IN CORONARY ARTERIOSCLEROSIS WITH MYOCARDIAL INFARCTION BY COMPARISON WITHIN PROGNOSTIC CATEGORIES. *Robert H. Furman, M.D., Robert G. Gale, M.D., F. Tremaine Billings, Jr., M.D. and George R. Meneely, M.D., Nashville, Tennessee.*

From the Department of Medicine, Vanderbilt University School of Medicine and the Research Laboratory, Thayer Veterans Administration Hospital.

It is possible to sort patients with myocardial infarcts into categories according to the nature of the clinical manifestations observed. When this is done, patients in some categories fare very much worse or very much better than would be expected of the group as a whole. It would appear that comparison within prognostic categories was a more valid method of investigating the effect of anticoagulant therapy than by application of overall mortality rates. The purpose of this presentation is to report certain tentative conclusions which may be inferred from a preliminary analysis of 343 patients with attacks of myocardial infarction of whom 240 were a sample from our past experience, eighty-two had recently observed episodes treated with anticoagulants and twenty-one had recent episodes not so treated. These three groups of patients were comparable as to age, sex and severity of illness.

The mortality among controls was 40 per cent, among anticoagulant-treated patients 16 per cent. Closer scrutiny showed, however, that the reduction was almost entirely due to a reduction in mortality among those suffering from first attacks. The outlook for the patient in an attack other than the first attack was not modified by anticoagulant therapy. Thrombo-embolic manifestations among our control patients were uncommon. We could not, therefore, account for lowered mortality on the basis of prevention of peripheral or pulmonary thrombo-embolic

phenomena. Among control patients with congestive heart failure the outlook was ominous but anticoagulant therapy sharply improved the gloomy prognosis from an expected mortality of 55 per cent to 17 per cent. Even in the presence of a shock-like syndrome, the mortality was lowered. So also in the case of cyanosis or leukocytosis the application of anticoagulants resulted in sharply lowered thirty-day mortality.

CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN NEUROSYPHILIS. *John L. Patterson, Jr., M.D. (by invitation) and Albert Heyman, M.D., Atlanta, Georgia.*

From the Departments of Physiology and Medicine, Emory University School of Medicine.

The cerebral blood flow in a group of patients with neurosyphilis has been determined by means of the nitrous oxide technic of Kety and Schmidt. Cerebral oxygen consumption has been calculated utilizing the flow data and the arteriovenous (internal jugular) oxygen differences.

In patients with paresis and meningovascular syphilis the cerebral blood flow was found to be below the normal mean in almost every instance. In some patients with paresis the cerebral blood flow was decreased by as much as 50 per cent of normal. Cerebral oxygen consumption was reduced in both groups of patients but the reduction was considerably greater in paresis. With few exceptions the cerebral blood flow and oxygen consumption were normal in asymptomatic neurosyphilis.

The effect of penicillin and fever therapy was determined in a number of these patients. Following treatment the mean cerebral blood flow was essentially unchanged in paresis but was significantly increased in meningovascular syphilis. The cerebral oxygen consumption increased markedly both in patients with paresis and in those with meningovascular syphilis. The changes in cerebral blood flow and oxygen consumption in a given patient could be correlated to some degree with the clinical improvement.

These alterations in cerebral blood flow and oxygen consumption are believed to be the result of the vascular and parenchymal changes produced by syphilis of the central nervous system.

A COMPARISON OF GLOMERULAR AND TUBULAR PLASMA FLOW IN MAN. *Walter H. Cargill, M.D. (introduced by James V. Warren, M.D.), Atlanta, Georgia.*

From the Departments of Medicine and Biochemistry, Emory University School of Medicine.

The rate of plasma flow through the kidney may be calculated from the rate of excretion of a substance and the concentration of this substance in arterial and renal-venous plasma,

according to the formula $\frac{UV}{A - R}$. The available

evidence indicates that inulin is excreted entirely by glomerular filtration, whereas the excretion of sodium para-aminohippurate is accomplished largely by active tubular transfer. The value for renal plasma flow obtained from inulin concentrations should represent, therefore, only the volume of plasma which perfuses the glomeruli, and that derived from para-aminohippurate clearance and extraction represents the flow through both glomeruli and tubules, predominantly the latter. These determinations therefore may be designated glomerular plasma flow (GPF) and tubular plasma flow (TPF).

We have compared glomerular and tubular plasma flows in normal subjects and in patients with glomerulonephritis or nephrosclerosis who had varying degrees of renal impairment. Samples of renal venous blood were obtained by the technic of intravenous catheterization.

Close agreement between GPF and TPF was found in all subjects, indicating that inulin is neither metabolized nor stored by the kidney and that there is no extensive dissociation of glomerular and tubular blood supply even in advanced renal disease.

MECHANISMS OF PHASIC PAINS INDUCED BY COLD. *E. Charles Kunkle, M.D., Durham, North Carolina.*

From Duke University School of Medicine.

Cyclic pain and other phenomena induced by immersion of a finger in cold water have been analyzed in 130 experiments upon twenty-four adult subjects. At a water temperature of 0°C. the initial pain, a deep cold ache, rises usually to a high intensity in three to five minutes, at which time plethysmographic records indicate the arteries of the immersed finger are extremely constricted. This "first" pain then slowly

subsides, an "adaptation" accompanied by progressive impairment of sensation in the chilled digit and by a partial release of the local vasoconstriction.

The onset of a "second" pain after eight to twelve minutes is foreshadowed by a brisk further increase in local circulation and by a rapid return of sensibility in the digit. At the peak of "second" pain, a burning ache, the digital pulse amplitude is well above control levels. With the rapid subsidence of this pain, the pulse amplitude falls to normal and the finger remains fully sentient.

If the digit remains in the bath thereafter, for periods up to two hours, additional recurrences of pain are noted; each such phase is usually brief and mild accompanied by moderate vasoconstriction. Upon removal of the finger from the bath after "first" or "second" pain, a transient but intense "after" pain is commonly noted, accompanied by hyperemia and similar in quality to "second" pain.

The analysis of vascular components in the pain mechanisms is aided by interruption of circulation to the hand at strategic points in the cycle. The data suggest that vasoconstriction, which previously had been assumed to be in itself the source of cold pain, is relevant mainly in promoting cooling of the finger and thus intensifying the pain stimulus. It is also inferred that "adaptation" to "first" pain is a complex of reactions involving (1) impairment of sensory transmission and (2) rewarming of chilled tissues by release of vasoconstriction. The return of full function in sensory nerves earlier numbed by cold leads to "second" pain; an additional contribution to this pain may come from excessive dilatation of digital arteries. These phenomena are relevant to the experience of the patient with Raynaud's disease in whom, because the digits are prone to vasospasm, there is unusual vulnerability to pain during and after chilling.

CINERADIOGRAPHY IN MAN. *J. V. Warren, M.D., H. S. Weens, M.D. (by invitation), R. L. McWhorter, Jr., M.D. and H. L. Murray, M.D., Atlanta, Georgia.*

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The development of a means for recording an x-ray image by motion pictures, cineradiography, has been hampered by various technical

difficulties. Since many body activities occur quite rapidly, slow motion filming is desirable but increases the technical problems. Recent reports from this laboratory have described a cineradiographic method for the study of small animals. This technic has been modified to provide a relatively simple and practical method for cineradiography in man.

The so-called indirect method is employed in which the image produced on a fluoroscopic screen is photographed with a motion picture camera. An x-ray generator of high energy output is used in conjunction with a heavy duty rotating anode tube. The fluoroscopic screen is incorporated in one side of a telescopic, light-tight wooden box. The opposite side of the box is a sheet of lead through the center of which there is an aperture for the camera lens. Both 16 and 35 mm. motion picture cameras with large aperture lenses and high speed film have been used. This apparatus permits the photographing of the fluoroscopic image in an illuminated room and gives considerable flexibility in operation. Measurements have shown that the radiation received by the patient is not excessive providing the exposure is not prolonged.

Studies already carried out demonstrate several possible fields of application. The motions of bones and joints can be clearly recorded. By making slow motion films during the swallowing of a barium mixture, the passage of the bolus through the pharynx and esophagus can be observed. Cine-angiocardigrams (films of the heart and great vessels during the injection of contrast media) have also been made. In addition to providing a means of actually visualizing the passage of the material through the heart and great vessels frame by frame analysis provides a means of accurately studying various events in the cardiac cycle.

DIFFERENTIATION OF THE CONTINUOUS MURMUR OF PATENT DUCTUS ARTERIOSUS FROM THE TO AND FRO PULMONIC MURMUR. *A. L. Hyman, M.D., Louis Levy, II, M.D., Edgar Hull, M.D. (by invitation) and Richard Bagnetto, M.D., New Orleans, Louisiana.*

The presence of a patent ductus arteriosus must be considered when a systolic and diastolic murmur are heard at the second left intercostal space; however, there are certain characteristics which differentiate the continuous murmur of a

patent ductus arteriosus from the to and fro murmur produced by pulmonary artery or valvular disease.

The to and fro murmur heard in five patients with pulmonary valve or artery disease is contrasted with the continuous murmur produced by patent ductus arteriosus. These patients had cardiac catheterization and peripheral arterial oxygen studies in addition to routine work-ups including sound tracings. One patient had congenital isolated pulmonary valve stenosis and insufficiency, two had acquired congenital isolated pulmonary valve stenosis and insufficiency, one on a rheumatic and one on an endocarditis basis, and two patients had pulmonary artery aneurysms.

The machinery murmur of a patent ductus arteriosus is continuous throughout systole and diastole in most cases. It may occasionally fade out in late diastole; however, it should almost always tend to continue past and obscure the second sound. On the other hand, a to and fro murmur found in pulmonary artery and valvular disease consists of a systolic crescendo murmur, usually a second sound, and a diastolic decrescendo murmur with a pause between the two phases. The continuous murmur tends to have the same quality throughout with increased intensity in systole, whereas the to and fro murmur usually tends to be low-pitched and rough in systole and high-pitched and blowing in diastole.

PRELIMINARY STUDIES ON THE ASSAY OF LACTOGENIC HORMONE IN HUMAN URINE.

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From the Departments of Physiology and Medicine of the Tulane University of Louisiana and the Endocrine Research Laboratories of the Alton Ochsner Medical Foundation.

Riddle and Bates have shown that the weights of excised crop-sacs of pigeons are proportional to the amount of systemically administered prolactin. The local method of Lyons, modified by Hall, compares the two crop-sacs of the same pigeon after intradermal injection of a known prolactin standard over one sac and an unknown over the other.

In our procedure, prolactin was extracted from twenty-four-hour urine specimens by multiple acid-alcohol precipitations and dialysis against 0.5 per cent saline. Assay by the local technic, at first the only method used, did not prove entirely satisfactory as the prolactin response was often obscured by a non-specific inflammatory reaction. Systemic assay, employing intravenous injection, gave results which correlate satisfactorily with those of local assay. In both methods injections were made daily for four days and the animals were sacrificed on the fifth day.

Local assays on four normal women revealed a urinary prolactin excretion of < 25 I.U. to 100 I.U./24 hours, with no consistent change accompanying various phases of the menstrual cycle; of these subjects two nulliparae were consistently lower than two who had borne children. One male had values of 50 and 100 I.U./24 hours.

Assays by the local technic revealed assayable values within the range of our few normals in three cases of pituitary tumor, in hirsutism (two cases), precocious puberty (one) and advanced breast carcinoma (five). Low values were obtained in three patients with fibromyomata uteri, in endometriosis (one), bilateral testicular atrophy (one), Sheehan's syndrome (one) and breast carcinoma (two). Elevated values were found in Cushing's syndrome due to adrenal carcinoma (one case), precocious puberty (one), chronic cystic mastitis (one) and breast carcinoma (two).

Case Reports

Chronic Pancreatitis*

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PANCREATIC disease is still surrounded by mystery. The present concept of the pathologic physiology of acute pancreatitis is at best a working hypothesis. The changes seen at operation vary from slight edema to severe fat and vascular necrosis and are thought of as resulting from varying degrees of duct obstruction. Such obstruction, with or without attendant infection, is considered responsible for the escape of lipolytic and proteolytic enzymes into the interstitial tissue of the gland and into the surrounding tissues.

The causes of the obstruction are frequently obscure. Evidence to support the "common channel" hypothesis, which is anatomically possible in about 50 per cent of cases, is not often found. Metaplasia of the epithelium of the ducts apparently does not answer the question either in the majority of cases although perhaps it is not looked for with sufficient diligence. An unduly thick and viscous type of mucus has been shown to cause the obstruction in the chronic cystic fibrosis of infants and children but has never been demonstrated in adults.

The exact mechanism by which the enzymes escape from the ducts is equally obscure. Pressures built up by glandular secretions are not enough to produce rupture of even the smallest ducts. The answer to the problem may lie in the fact that the active part of the enzyme is loosely bound to a large colloidal carrier. Ågren¹ has suggested that under conditions of increased acidity, increased enzyme concentration and increased pressure it is possible that the small active group becomes

dissociated from its carrier and passes through membranes into the capillaries and into the interstitial spaces where it then finds another carrier. Such a method of passing through tissue barriers has been demonstrated in other enzyme systems.

Chronic pancreatitis appears in forms even more difficult to bring together into a single dynamic concept. Recently Comfort² has written an excellent review of a syndrome which he calls chronic relapsing pancreatitis. The term indicates repetitive attacks of pancreatic pain, with or without such signs of acute inflammation as fever, leukocytosis and elevated serum amylase or lipase. Sooner or later the results of destruction of the gland may occur in the form of steatorrhea, diabetes or calcification. This picture describes the natural history of an organ affected by disease processes. It focuses attention on a clinical syndrome rather than on individual pathologic entities and thus corresponds to the concept of Bright's disease as contrasted with the various forms of nephritis.

Certain types of chronic pancreatitis vary sufficiently from each other to warrant a tentative separation. Although an obstructive factor may underlie all forms, variations in the type and location of the obstruction may be responsible for varying clinical and pathologic pictures. Thus there are the various kinds of cysts which are sufficiently large to become surgical problems. There is the mass of fibrous tissue which simulates carcinoma not only in its clinical manifestations but even at operation and on frozen section. There is the pancreatic lithiasis

* From the Department of Medicine, Veterans Administration Hospital, Topeka, Kan. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn.

which behaves very much like its counterpart, cholelithiasis, in that symptoms may be present or absent. And there is the childhood form known as chronic cystic fibrosis.

Recently another type has been separated tentatively from the hodgepodge of chronic diseases of the pancreas. This has been termed "disseminated calcification of the pancreas," and Wirts and Snape³ have written a good review of the subject. In general the symptoms and signs are those of chronic relapsing pancreatitis: attacks of epigastric pain, manifestations of insufficiency of various functions of the gland and evidence of fine stippled calcification. The picture may differ, however, from the usual pancreatic lithiasis in several ways: (1) Its incidence is much lower. The incidence of pancreatic lithiasis of all types is hard to determine because it will vary with the interest of the observer. Thus in several large series of routine autopsies the figures are given as from 0.04 per cent to 0.1 per cent whereas if x-rays and careful dissection are done the incidence rises to something over 5.0 per cent. Only twenty-five cases of "disseminated" pancreatic calcification have been reported as such, but this is not a true measure of its incidence as some authors² have not considered it a separate entity. (2) It has been stated that the calcification occurs at a somewhat younger age than the usual pancreatic lithiasis. Again exact figures are hard to gather because the age at which symptoms began is not always given in reports. (3) The calcification as seen by x-ray is a diffuse stippling or mottling involving various portions of the gland. It is thus quite different from the typical pancreatic lithiasis which is described usually as multiple calculi irregular in shape and size, occasionally as single calculi or multiple faceted calculi and rarely as casts of the ducts. (4) Biopsy and autopsy specimens show extensive replacement of the parenchyma by fibrosis, with varying degrees of dilatation of the larger ducts and more constant dilatation of the finer ducts. The minute calculi extend

throughout the duct system into the finest radicles. Occasionally larger calculi are present in the larger ducts. Further careful histologic studies will be necessary to determine whether this picture actually represents a disease process distinct from the more usual type of lithiasis and from other forms of chronic pancreatitis without calcification. For the present it would seem worth while to consider it a different disease process.

The following case is an example of this type of chronic pancreatitis. It illustrates almost all the points which various authors have made about chronic pancreatic disease. In particular it shows the difficulties of establishing the diagnosis and how the effect of long continued "hidden" pain can produce a picture practically indistinguishable from a psychoneurosis.

CASE REPORT

D. M., a thirty-five year old white male, was admitted to the Veterans Administration Hospital, Topeka, Kansas, in August, 1946 because of a psychosis due to bromide intoxication.

His past history was not remarkable. There had been the usual childhood diseases, including pertussis and mumps, and the usual number of respiratory infections. He had been somewhat "scrawny" but in general his physical health had been good. Emotionally, however, his childhood had been rather stormy. His parents separated when he was eight months old and he lived with his mother and grandmother. There were frequent arguments and frequent moves from one place to another. Later, during the depression years, the patient worked at many different jobs and was unemployed at times. He was twice married. The war came along when for the first time he was beginning to have a feeling of some security in his job and married life.

At the Army induction examination in 1942 the rack of blood tubes was dropped and no attempt was made to recall the men. In 1943 a Wassermann test taken during a routine examination was positive. At this time his wife and child were checked and were negative. He was advised that he had congenital syphilis and that no treatment was indicated. On separation from the Army his Wassermann test was

again positive. During his military service he made a good record and became a technical sergeant. From May, 1943 to June, 1945 he was in the China-Burma-India Theater of Operations. During this period he began to notice vague abdominal aching and discomfort. This gradually became more bothersome and was associated at times with equally vague symptoms of "indigestion." On two occasions the pain became severe enough to require hospitalization. During the second hospitalization in the spring of 1945 he received the usual investigative studies, including stool examinations and a gastrointestinal x-ray. He was told that his pain was due to a psychoneurosis.

Following his separation from the service in September, 1945, his wife left him and he became somewhat depressed. Shortly thereafter he was hospitalized with pneumonia in the Veterans Administration Hospital, Wadsworth, Kan. Here he was found to have positive serologic tests for syphilis in both blood and spinal fluid. After the pneumonia cleared he was therefore held for malarial therapy but a chronic productive cough persisted. Because of this, malarial therapy was deemed inadvisable and he was given 6 million units of penicillin.

While he was still in the hospital, he developed a pleural type of pain in his lower posterior chest, sometimes on one side and sometimes on the other. He also developed a deep, aching substernal pain, diffuse in character, and referred at times to the left shoulder and throughout the ulnar nerve distribution of the left arm. This substernal pain seemed to represent an upward spread of the abdominal discomfort which had been present to some degree for the previous two years. It was apparently related to his esophagus because fluids seemed to "stick in his throat" at times, with accentuation of the pain. Solid food was chewed well and swallowed without discomfort but he was inclined to gulp his fluids. Belching relieved the pain to some degree.

On leaving the hospital in March, 1946 his condition was as follows: he had a chronic, somewhat productive cough; mild to moderate radicular pain in the lower posterior chest; mild abdominal discomfort and mild to severe substernal aching with ulnar radiation at times; he was weak and he tired easily.

Shortly thereafter he received from a private physician a prescription for neurosine which he continued to take in steadily increasing

amounts without further medical advice. In August 1946 he became confused, quit his job and was picked up a few days later wandering about the streets of Kansas City in a completely disoriented state. He was admitted to the Veterans Administration Hospital, Topeka, Kan., two days later. He was confused and disoriented and showed bizarre neurologic findings. The blood bromide level a few days later was 175 mg. per cent. Serologic tests for syphilis were again positive in both blood and spinal fluid; the spinal fluid protein was 126 mg. per cent and the colloidal gold curve 0001221000. An x-ray of his chest showed increased bronchovascular markings in the lower lung fields which were more noticeable on the right side. Other routine examinations showed no abnormalities.

A month later the psychosis had entirely disappeared and the patient was transferred to the medical service. Here he was given another course of penicillin, 4.8 million units, and subjected to that somewhat nebulous regimen known as building-up. Because of his continued complaints, chiefly of radicular and substernal pain, he was thought to be psychoneurotic and therefore transferred to the open-ward psychiatric service. Here certain psychologic abnormalities were elicited such as fear of being watched, fear of being in groups, fear of having people behind him, undue dependency on his mother, a tendency toward alcohol and drug addictions and gastrointestinal symptoms. It was thought that these symptoms existed prior to military service and had been aggravated by his period of service. He was presented at a psychiatric conference and a diagnosis of psychoneurosis, mixed type, was made.

In November, 1946 his father died and the patient was furloughed for ninety days. He returned to the hospital in February, 1947, prior to the date of expiration of the furlough, acutely ill, coughing up a moderate amount of bright red blood and with signs of fluid at the base of his left lung. His temperature was 101°F. and the leukocyte count 16,800. Thoracentesis yielded clear brownish fluid in which a filmy reddish web formed on standing. The white cell count of this fluid was 468 with 98 per cent polymorphonuclears. Both smear and culture were negative. The reddish color of the fibrin web was due to the presence of red blood cells entangled in its strands, and the brownish fluid gave a strong positive reaction with benzidine. X-ray of the chest showed a moderate amount

of fluid on the left and the previously noted accentuation of the bronchovascular markings on the right.

In the subsequent month his chest cleared. He continued to have episodes of hemoptysis and fever but these progressively decreased in severity and after three months ceased entirely, leaving only the chronic cough which had been present for two years. At this point he presented quite a diagnostic problem. The clinical impression was that he had bronchiectasis but lipiodol bronchograms showed no evidence of this, in the lower lobes at least. Bronchoscopy, done unfortunately at a time when he was not bleeding, was equally negative. Because of the hemoptysis and pleural fluid with some blood in it plus his stay in the Orient, the possibility of paragonimiasis was entertained, but repeated searches of sputum and stools failed to show any ova. Smears and cultures were likewise negative for tuberculosis and pathogenic fungi.

Throughout this period the radicular pains in the lower posterior chest had persisted. Two bands of mild hyperesthesia were demonstrable, one from the fourth to the eighth thoracic and a more pronounced one from the eighth to the twelfth thoracic vertebrae. The substernal aching had likewise persisted and at times had been severe. The character of this pain, its radiation to the neck and left arm and its association with a feeling that a belch was imminent made it relatively certain that it was due to esophageal spasm. Repeated electrocardiograms were normal and the pain was not related to exertion. To a certain degree emotional disturbances seemed to aggravate the pain. Belladonna in doses to tolerance seemed to lessen its severity but did not abolish it. A gastrointestinal series showed normal mucosal markings in the esophagus, no evidence of cardiospasm or hiatus hernia and a normal stomach and duodenal cap. Stippled calcification was noted in the left upper quadrant and interpreted as a mesenteric node. Esophagoscopy during an episode of pain was indicated but was not feasible. Spinal fluid examination nows honed no abnormalities. Because he was obviously ill he was kept in the hospital although no diagnosis had been established.

Psychologic testing was carried out utilizing a battery of six tests. In summary, these showed a very intelligent, mildly neurasthenic person with some tendency toward compulsiveness and with some introversive trends. The presence of

an underlying psychosis or severe neurosis was not indicated. In essence he was as "normal" as most of us and probably more so than many of us. When questioned about the previously elicited psychoneurotic symptoms, such as fear of being watched and so forth, he replied, "Why, everybody feels some of those things at some time during their life. I was convinced I was a psychoneurotic, and they asked me about those things so I told them."

Toward the end of April, three months after re-admission, his sedimentation rate (Wintrobe method) rose to 30 and his white count to 15,000. Two weeks later he suddenly developed severe, constant, upper abdominal pain which lasted for ten days and then disappeared as suddenly as it had come. The patient said that this was exactly like the two previous episodes he had had in China three years previously. The pain was not sharply localized but was felt in the upper abdomen a little to the left of the midline. It radiated through to the back at about the level of the third lumbar rather more on the left side than the right. The pain was very severe at times and was relieved only by opiates. During the first five days of the ten-day period there was considerable vomiting, and intermittent nausea and severe constipation persisted throughout. For three days, about the middle of the attack, his temperature rose to 100 to 101°F. At no time was the abdominal examination remarkable, save for constant deep tenderness in the left upper quadrant.

Within a week after the sudden termination of the abdominal pain, he began to notice gradually increasing thirst and increasing frequency of urination. After two weeks this became sufficiently marked so that he complained of it. His urine sugar was then found to be 4 plus and his fasting blood sugar 348 mg. per cent. He was placed on 20 units of protamine zinc insulin which at that time adequately controlled the diabetes. It now appeared that the patient must have pancreatic disease and that this could explain the whole picture.

Further x-ray studies showed a normal functioning gallbladder and normal renal shadows by the intravenous method. A small intestinal study revealed a marked abnormality in the jejunum and ileum, with segmentation, loss of mucosal markings, areas of spasm and of dilatation, "puddling" of the barium and slight delay in gastric emptying. Films in various positions showed the previously noted area of

diffuse mottled calcification in the left upper quadrant and in addition another similar area overlying the second lumbar vertebrae just within the curve of the first and second portions of the duodenum. (Fig. 1.) The two areas of disseminated calcification lay, therefore, within

TABLE I
RESPONSE TO SECRETIN—THE FIGURES REPRESENT THE
TOTAL OUTPUT FOR AN EIGHTY-MINUTE PERIOD
FOLLOWING INTRAVENOUS INJECTION OF SECRETIN,
1 UNIT PER KG.

	Vol. cc./Kg.	Bicar- bonate m.Eq./ L.	Trypsin (units/ Kg.)	Amy- lase*	Lip- ase†
Control					
Case. . . .	5.3	118	1.45	9.4	1570
Patient. . . .	1.2	12	0.24	0.49	89

* Amylase figures represent Gm. of dextrose liberated.

† Lipase figures represent the volume of N/10 base required to neutralize butyric acid liberated from tributyrin substrate.

the area occupied by the pancreas, one in the region of the head and the other somewhere beyond the mid-portion. Repeated stool examinations showed a rather soft and mush-stool of normal color and in no sense foamy or oily. Microscopic examinations, however, constantly showed a moderate amount of free fat, numerous fatty acid crystals and frequent particles of undigested meat fibers. Blood cholesterol was 261 mg. per cent; calcium, phosphorus and phosphatase determinations were within normal limits; cephalin-cholesterol flocculation test was negative. Blood amylase and lipase determinations were done repeatedly, particularly at the onset of subsequent attacks, but they were always normal. A secretin test showed very marked diminution in all the functions of the gland. The test was carried out according to the method of Ågren,^{1,4} using a double lumen tube so as to maintain constant gastric as well as duodenal aspiration. This not only eliminates the stimulating effect of gastric acid on pancreatic secretion but also provides a means of checking on any possible reflux of duodenal contents into the stomach. (Table I.)

He was given pancreatin 10 Gm. daily, large doses of the fat-soluble vitamins, and a "sprue" diet high in protein and free sugar and low in starch and fat. At any given time the diabetes

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FIG. 1. Right anterior oblique view showing diffuse stippled calcification in the head and body of the pancreas.

could be well controlled with insulin, but successive bouts of abdominal pain, anorexia and vomiting necessitated frequent drastic shifts in both diet and insulin.

He was again furloughed in September, 1947 but another attack of pain in October necessitated hospitalization this time in the Veterans Administration Hospital, Montgomery, Ala. Physical findings were essentially unchanged and a bronchogram was again normal. Bilateral sympathetic block with procaine from the tenth thoracic to the first lumbar vertebrae, inclusive, afforded complete relief of pain for three hours. A subsequent block from the eighth to the tenth thoracic vertebrae gave very little relief.

The patient returned to the Veterans Hospital, Topeka, in December, 1947, with the clinical picture unchanged save that he now required 40 to 50 units of insulin to control his diabetes. Abdominal pain continued to occur at intervals of a few weeks. Between attacks he was asymptomatic save for the constant mild back pain. For several days he had swelling and tenderness of both submaxillary glands as well as a rather dry mouth. He stated that this was the third such episode. X-rays of the glands showed no abnormalities.

COMMENTS

Without entering into a discussion of all the problems concerned, I would like to stress certain points:

1. Pancreatic pain may be present for years without demonstrable abnormalities revealed by routine methods of examination. There are several reports in the literature of patients who were erroneously considered to be psychoneurotic, a mistake which is particularly likely to occur when emotional disturbance is suggested by the life history or by the presenting personality of the patient.⁵⁻⁹ Pratt¹⁰ states that he returned five such patients to referring physicians as psychoneurotics before he became sufficiently aware of the hidden nature of pancreatic disease. The vagaries of the pain itself contribute to the likelihood of such an error. It is described as characteristically a deep boring epigastric pain occurring in attacks over months or years, with nausea and vomiting, usually unassociated with meals, often aggravated by alcohol and requiring morphine for relief. But the pain may be a constant dull ache in the epigastrium or left upper quadrant or it may be felt primarily in the back. It may be in the right upper quadrant and may radiate to either of the lower quadrants. Involvement of a particular portion of the gland is presumably responsible for these distributions. Thus disease in the tail of the pancreas is often associated with pain which radiates upward into the substernal region and the ulnar distribution of the left arm. In some instances eating will aggravate the pain, and occasionally the associated reflex disturbance of the gastrointestinal tract may be so striking that comparatively mild pancreatic pain is overlooked. The pain is usually not a colic but a steady plateau type of deep pain. What actually causes the pain remains a complete mystery. A suggestion arises from pathologic studies of the gland which have shown a perineural inflammatory process at times.

2. The frequent association of alcoholism with chronic pancreatic disease is often commented on. Among alcoholics in gen-

eral, evidence of pancreatic disease is more frequent at autopsy than among non-alcoholics. It remains a moot question as to whether alcoholism has a specific effect on the gland or is damaging because of associated vitamin deficiencies. Alcohol is said to be a potent stimulus to pancreatic secretion but I am aware of no studies to show whether its effect is primary or secondary due to its stimulating effect on gastric acid secretion.

3. Several authors have stressed the fact that calcification may not be seen on a routine "flat plate" of the abdomen. In this instance the calcification in the body of the pancreas was dismissed, first as barium in the jejunum and later as mesenteric nodes. The calcification in the head overlay the vertebral bodies and was not seen. Oblique and lateral films are necessary as well as postero-anterior films taken with specific technics to bring out small areas of calcification. Most students of the problem consider stone formation the result and not the cause of the disease. This accords with general views on stone formation elsewhere in the body but does not imply that the presence of the stone may not be responsible for subsequent further damage.

4. The abnormal small intestinal pattern by x-ray, which goes by the very inadequate name of "deficiency pattern," has been described many times, particularly by Golden¹¹ and Mackie.¹² It is found characteristically whenever fat absorption is impaired for any reason, whether due to enzyme deficiency in pancreatic disease, bile deficiency in obstructive jaundice or "X" deficiency in sprue. But at times it is also found in such apparently unrelated conditions as experimental B complex deficiencies, nephrosis, mesenteric lymphadenitis and intra-abdominal carcinoma. In dogs it can be produced by plasmapheresis. In rats a state of rage is accompanied by the "deficiency pattern." It occurs normally in the newborn infant. Recently it has been found to occur very frequently in gastrointestinal disturbances of psychogenic origin. In certain instances

prostigmine will produce a return to a normal pattern. The so-called "deficiency pattern" therefore represents what is probably a disturbance in motility resulting from many different causes.

5. Chronic cystic fibrosis of the pancreas is a disease of infancy and childhood. Clinically, the patients are divided into three groups; (1) those dying within the first few weeks of life of meconium ileus, (2) those dying in the first year of bronchitis, bronchiectasis or pneumonia but with nutritional disturbances in the background and (3) those surviving longer and developing the picture of coeliac disease to a greater or lesser degree but dying of respiratory disease. (Pancreatic deficiency due to congenital abnormalities such as stenosis or atresia of the duct forms a separate group.) Pathologically, these cases show dilatation of the ducts, inspissation of secretions, acinar atrophy and fibrosis. The liver shows the fatty changes so frequent in pancreatic disease and rarely an unusual form of biliary cirrhosis which resembles the pancreatic changes. Inspissation of secretions in ducts and acini of other glands is found if specifically looked for. It is found in the salivary glands, in the mucous glands of the tracheobronchial tree, esophagus, and gall-bladder and is "so frequent it must be regarded as a characteristic feature of the disease."¹³ The theory of a primary disorder in glandular function is supported by the fact that cases of proven pancreatic deficiency with the coeliac syndrome may show at autopsy only inspissation, without fibrosis, atrophy or dilatation of the ducts. Blackfan has suggested that this syndrome may be due to an abnormality of the parasympathetic system, with production of an unusually thick secretion in various glands.

The inference that the primary changes in disseminated calcification of the pancreas occur in the small ducts, as evidenced by the location of the calcium deposits, has suggested to Wirts³ and others that this may represent a milder and long continued form of the childhood disease. The variations in

the childhood form which have been pointed out, particularly the third or oldest group, suggest that logically there should be a fourth group in which the disease process goes at an even slower rate, producing symptoms only in later life. Bronchiectasis has been looked for with this in mind but has not been found. Pulmonary disease in general, however, occurs in high incidence in the disseminated calcification group.

Certain symptoms in the present case support such an analogy. Bronchiectasis was never demonstrated, in the lower lobes at least, but the clinical picture was very characteristic. Certainly the patient had had a chronic lower respiratory tract abnormality for the previous two years. Likewise, the bouts of submaxillary gland swelling with episodes of dryness of the mouth suggest an abnormality of the salivary glands.

It was believed that syphilis was not responsible for the pancreatic disease in this case for several reasons, chief among them being the absence of syphilis in similar cases.

6. The therapeutic management of the trio of (1) episodic pain with vomiting, (2) pancreatic deficiency and (3) diabetes is difficult. Addiction is a constant problem because significant relief of pain is obtained only with generous doses of opiates. The various antispasmodic drugs, even in large doses, are of no use whatever. Fat absorption can be materially increased by pancreatin; the industrial detergents may prove of equal or greater value.¹⁴ Diet and hence insulin requirements may be in a constant state of flux if attacks with vomiting occur with any frequency. The only reported case in which the rational procedure of severing the sensory fibers of the pancreas was carried out is that of Reinhoff and Baker.¹⁵ Bilateral sympathectomy from the fifth thoracic to the second lumbar ganglion, together with vagotomy, provided complete relief of pain and changed a chronic addict of years' standing with a "psychopathic personality" back into a useful citizen. To date our patient has refused

operation although his course for the past two years has been that of a totally incapacitated invalid.

SUMMARY

A case of disseminated calcification of the pancreas is reported. The question of justification for such a clinical entity is briefly discussed and its possible relationship to chronic cystic fibrosis of childhood is considered. The case demonstrates certain aspects of chronic pancreatic disease in general which are of importance, such as the frequent confusion with psychoneurosis, the ease with which the diagnosis may be missed by x-ray and the difficult therapeutic management of the fully developed symptom complex.

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Megaloblastic Bone Marrow in Liver Disease*

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MEGALOBLASTIC bone marrow is found characteristically in patients with Addisonian anemia. The same type of bone marrow has been found also in association with macrocytic anemias of tropical and non-tropical sprue, idiopathic steatorrhea, celiac disease, pernicious anemia of pregnancy, "tropical" or nutritional macrocytic anemia and in some instances of intestinal strictures and fistulas between the different loops of bowel. Added to this list is a rare type of macrocytic anemia which has all the hematologic aspects of pernicious anemia, including megaloblastic bone marrow, but differing from the classical Addisonian anemia by absence of glossitis, achlorhydria, gastrointestinal disturbances and central nervous system involvement. The course is chronic and progressive in spite of liver therapy. The name of achrestic anemia has been given to this disorder on the hypothesis that the condition in these cases was the result of failure to utilize the antipernicious anemia principle.¹ Recently megaloblastic bone marrow has been described in certain cases of macrocytic anemia of an unknown non-dietary deficient etiology observed in infants under one year of age.²

Megaloblastic anemias may be classified etiologically into several main groups. The orientation for this classification is based on Castle's hypothesis of normal erythropoiesis. It will suffice to mention briefly that according to this hypothesis the maturation of the primitive erythroblasts is dependent upon the presence of an "anti-anemic principle" which is elaborated in the stomach from the interaction of an "intrinsic

factor" secreted by the gastric mucosa with an extrinsic factor present in certain protein constituents of the diet. The anti-anemic principle is believed to be absorbed in the upper part of the small intestine and is presumably stored in the liver. It has been suggested by some investigators³ that the liver may not act merely as a storage depot but may also participate in the final elaboration of the anti-anemic principle. It appears that some support for this assumption has recently been provided⁴ in the ingenious experiments with *Amblystoma* embryos in which removal of the liver anlage has been found to result in the development of anemia unaffected by liver therapy whereas the grafting of liver slices into the tails of the animals has resulted in restoration of hematopoiesis. The various etiologic classifications have been set up as follows: (1) Defective formation of the intrinsic factor; Addisonian pernicious anemia. (2) Defective intake of the extrinsic factor; nutritional anemias ("tropical" anemias). (3) Defective absorption of the anti-anemic principle; tropical and non-tropical sprue, idiopathic steatorrhea, celiac disease, gastrocolic fistula. (4) Defective storage and/or elaboration of the anti-anemic principle; liver disease, chronic (cirrhosis). (5) Defective utilization of the anti-anemic principle? "achrestic anemia," megaloblastic anemia in children.

Such a classification is, of course, provisional, in parts highly theoretical and subject to criticism. For example, under what category should one place the megaloblastic anemia of pregnancy and puerperium? Is it due to reduced intake of the extrinsic factor consequent upon poor appe-

* From The Veterans Administration Hospital, Oakland, Calif. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed and conclusions drawn by the author.

tite and nausea? Is it caused by impaired absorption of the anti-anemic principle from the small intestine due to altered hydrogen ion concentration of its contents? Or is it due to only a relative decrease in the amount of the available anti-anemic principle conditioned by the increased demand for it by the fetus?

The assumption that the liver plays an important role in the storage and possibly even in the elaboration of the anti-anemic principle would lead one to expect the occurrence of megaloblastic anemia in chronic hepatic disease. There are numerous references in the literature to macrocytic anemia found in association with chronic diseases of the liver, particularly cirrhosis. Wintrobe⁵ has found in a series of 132 cases of different forms of liver disease the presence of macrocytic anemia in 21.9 per cent, mostly in patients with cirrhosis. The bone marrow in these cases was described as hyperplastic although the red cell count was rarely below 2,500,000 per cu. mm. Wintrobe⁶ also stated that in some patients with diseases of the liver the anemia resembled that seen in Addisonian anemia and that "oval macrocytes like those seen in pernicious anemia are found." While it is now generally recognized that macrocytic anemia may be encountered in association with cirrhosis of the liver, the frequency of this finding varies in different reports. The red cell counts usually range from 2,500,000 to 3,500,000 per cu. mm.

In a recent report⁷ on nineteen patients with liver disease nine (47.4 per cent) had macrocytic anemia, six (31.6 per cent) normocytic anemia and four (21 per cent) had no anemia. Of the patients with macrocytic anemia four had atrophic and two hypertrophic cirrhosis, two had hepatitis and one carcinoma of the liver secondary to carcinoma of the pancreas. No patient in the entire series had nucleated erythrocytes in the peripheral blood and only one, who was believed by the authors to have sprue in addition to cirrhosis, had megaloblastic bone marrow. The red cell counts ranged from 2.80 to 3.99 million and the

intensity of the anemia was not related to the severity of the liver disease, but there was a positive correlation between the degree of macrocytosis and the patient's prognosis. Of the five patients with macrocytic anemia in whom gastric analysis was done only one showed histamine-resistant achlorhydria. One had achlorhydria which was not histamine-resistant and the others had normal gastric acidity. Interestingly enough, irrespective of the outcome of the liver disease, therapy with liver extract resulted in reduction of macrocytosis and increase in red cell count. Similar observations on the response to liver therapy have been reported by other workers.^{5,11,12} In patients with cirrhosis, macrocytic anemia has been found to be more severe than in the normocytic type except in instances of massive hemorrhage from the esophageal varices. Microcytic anemia found in some patients with cirrhosis may be attributed to chronic loss of blood.

In spite of the fact that the presence of macrocytic anemia in some patients with cirrhosis of the liver has become a part of common knowledge and that megaloblastic bone marrow could well be expected to be found in some of these patients, at least on theoretical grounds, reports to that effect have been lacking. Davidson and Davis⁸ state that "The literature contains many other references to macrocytic anemia in association with cirrhosis and other diseases of the liver, *but we know of no reports of the sternal marrow morphology in such cases.* References to the bone marrow seen at autopsy commonly refer to its being hyperplastic, but detailed cytologic descriptions do not appear to have been published." These authors make reference to the work of Higgins and Stasney⁹ and Shumacker and Wintrobe¹⁰ who have noted the production of experimental cirrhosis in animals to result in macrocytic anemia with a hyperplastic bone marrow picture stated to be similar to that seen in pernicious anemia without making it clear, however, whether it was actually megaloblastic. Davidson and Davis conclude that: "There appears,

then, to be presumptive evidence that a megaloblastic anemia may occur in chronic severe liver disease."

The author has had the opportunity of observing megaloblastic bone marrow in a patient with cirrhosis of the liver accompanied by severe macrocytic anemia. As the patient had free hydrochloric acid on gastric analysis, intact tongue papillae and failed to respond to liver extract the diagnosis of Addisonian pernicious anemia could not be entertained.

CASE REPORT

A fifty year old white male stated that he had been in good health until five months before admission when he developed an upper respiratory infection followed by pitting edema of the legs which would be present in the evening and disappear overnight. At the beginning of his illness he was first hospitalized elsewhere and was discharged eight weeks later. On leaving the hospital he still was rather tired and the edema of the legs, although not so marked as it was at the beginning of the illness, was still present and remained without much change until admission to this hospital. There were no significant gastrointestinal symptoms. The past history was not particularly remarkable except for chronic alcoholism.

On examination the patient was seen to be a well developed but undernourished white male of about the stated age with slight icterus of the sclerae. There was no atrophy of tongue papillae. The heart and lungs were not remarkable. There was no engorgement of the cervical veins. The blood pressure was 110/80, pulse 68. The abdomen was distended, with shifting dullness in the flanks. A firm, non-tender liver could be felt by ballottement. There was moderate pitting edema of both legs and several spider angiomas over the upper anterior chest. Neurologic examination was negative.

On admission the laboratory work revealed the following findings. Urinalysis: color, clear amber; reaction, acid; specific gravity, 1.009; albumin, negative; sugar, negative; sediment, some epithelial cells, a few white blood cells. A second urinalysis was also entirely negative. Red blood cells, 1.7 million; white blood cells, 6,150 with 73 per cent polymorphonuclear leukocytes (70 segmented and 3 stab forms); lymphocytes, 23 per cent (20 small and 3 large);



FIG. 1. Photomicrograph of the bone marrow smear showing megaloblasts.

monocytes, 1; eosinophils, 3. The blood smear showed some anisocytosis and poikilocytosis with slight polychromasia and stippling in addition to an occasional Howell-Jolly body. Reticulocyte count was 3 per cent. Erythrocyte mean corpuscular volume was 118 cu. microns and mean corpuscular hemoglobin was 38.5 micrograms. Icterus index was 21 units and serum bilirubin 3.0 mg. per cent. The Kahn test was negative. Blood urea nitrogen was 18 mg. per cent. Total serum protein was 4.8 Gm. per cent with albumin 2.7 Gm. per cent and globulin 2.1 Gm. per cent. Cephalin cholesterol flocculation was 2 plus in twenty-four hours and 3 plus in forty-eight hours. Bromsulfalein test showed 10.6 per cent retention of the dye in forty-five minutes (5 mg./Kg. dose). Gastric analysis after alcohol meal revealed the presence of free hydrochloric acid with 15 degrees as the maximum. Roentgenogram of the chest revealed nothing of note. The bone marrow aspirated from the sternum revealed megaloblastic proliferation,* (Fig. 1) with the following differential count: myelocytes, 15; metamyelocytes, 10; polymorphonuclears, 40; eosinophilic

*The bone marrow preparations were also studied by Dr. Harry Wyckoff (Stanford University School of Medicine) who confirmed our observations.

polymorphonuclears, 1; lymphocytes, 7; megakaryoblasts, 10; pro-erythroblasts, 4; normoblasts, 12; megakaryocytes, 1.

The patient was given liver extract intramuscularly, 30 U.S.P. units daily. However, as he failed to respond (Fig. 2) a blood transfusion

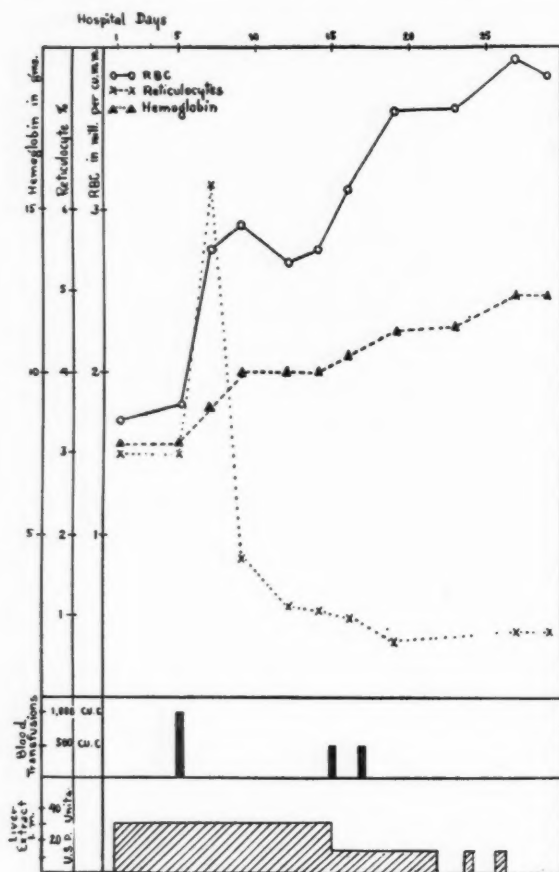


FIG. 2.

of 1,000 cc. was given on the fifth hospital day. The reticulocyte count following the transfusion went up to 6.3 per cent but soon dropped to 1.7 per cent. Liver therapy was continued in the same dosage but again without any response. Another blood transfusion of 500 cc. was given on the fifteenth hospital day and a third one of 500 cc. on the seventeenth hospital day. Further liver therapy still failed to produce any significant change.

COMMENTS

Although liver biopsy was not done, all clinical evidence pointed to a diagnosis of cirrhosis of the liver. One can only speculate about the pathogenesis of megaloblastic anemia associated with cirrhosis.

Is it due to nutritional deficiency, faulty absorption, failure of storage and/or elaboration or failure of utilization of the anti-anemic principle? Perhaps there is a number of factors operating concomitantly to produce the end result in question.

It has been suggested that patients with this disorder may suffer from the result of defective storage of the anti-anemic principle in the liver when a hepatic disease has been of a sufficient duration and extent to lead to significant depletion of the stores of hematopoietic principle. Observations have been made showing that the liver of a patient with macrocytic anemia who died of cirrhosis was ineffective in the treatment of a patient with pernicious anemia.⁵ On the other hand, other investigators have been able to demonstrate the presence of this principle in the liver of patients dying of extensive hepatic involvement.

Apparently megaloblastic bone marrow is not found in all the patients with cirrhosis and macrocytic anemia and possibly the anemia must be severe before megaloblastic arrest becomes evident on study of the bone marrow material. As severe megaloblastic anemia associated with cirrhosis is seldom encountered the unawareness of the existence of megaloblastic arrest in this condition can thus be explained.

True enough, cirrhosis of the liver and pernicious anemia may sometimes occur in the same individual. However, our patient did not appear to represent such a coincidence for the reason that he had free hydrochloric acid in the stomach, had no atrophy of the tongue papillae and failed to respond to liver therapy. The response to liver therapy in the case herein presented is somewhat difficult to evaluate. It is possible that were the treatment continued for a longer period and without blood transfusions it eventually would have proved to be more successful.

SUMMARY

Cirrhosis of the liver accompanied by severe macrocytic anemia constitutes another disease entity which can be added to the

list of conditions associated with megaloblastic proliferation in the bone marrow.*

Evidence has been presented indicating that in such cases this phenomenon does not necessarily represent the coexistence of two diseases, cirrhosis and pernicious anemia, in one and the same patient.

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- * Since submission of this manuscript for publication, another case of cirrhosis of the liver with megaloblastic anemia has come under our observation. In this patient the clinical diagnosis of cirrhosis was corroborated by the liver needle biopsy which showed extensive and far advanced fibrosis. There was moderately severe macrocytic anemia with a red blood count of 2.88 million and a hemoglobin of 11.1 Gm. There were 20 per cent megaloblasts in the sternal bone marrow material which was obtained by aspiration. In contrast to the other case herein reported this patient improved rapidly on minimal amounts of liver and a high caloric, high protein diet, with the blood count returning to practically normal limits within a short period of time. The patient had free hydrochloric acid in the gastric juice and gave no history of any gastrointestinal symptoms or glossitis.
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Epileptic Equivalents, A Cause for Somatic Symptoms

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THE internist is called upon many times to uncover the cause for pain.

In most cases, after adequate study, the diagnosis becomes apparent but there is a small group in which no explanation seems to be at hand and in which the diagnostic study must be extended to the limits of present scientific methods. The present praiseworthy emphasis upon psychic factors in the causation of symptoms introduces one danger, namely, that when all reasonable methods of study fail to reveal the cause for the patient's symptoms there is a temptation to decide that there must be a psychogenic cause. The cases herein reported illustrate not only this point but also the difficulties occasionally encountered in making the proper diagnosis.

That pain may occur as the sole equivalent of an epileptic convulsion has been pointed out by a number of writers. Penfield and Gage¹ showed that stimulation of a cortical area caused pain in the abdomen and elicited an epileptic attack. Watts and Frazier² found that a neurogenic discharge may manifest itself through abnormally vigorous movements of the gastrointestinal musculature and that the discharge comes from the autonomic portion of the cerebral cortex. Wechsler³ reported a series of cases which led him to conclude that abdominal pain occasionally occurs in disease of the brain and may be regarded as one of its manifestations. Moore⁴ has reported a number of cases presenting paroxysmal abdominal pain as an aberrant form of epilepsy and stresses in the diagnosis the exclusion of intrinsic visceral disease, the objective evidence of cerebral organic dis-

ease or dysfunction and the effect of anti-convulsant drugs on the symptom of abdominal pain and on the electroencephalogram. The following cases are of interest in this connection:

CASE REPORTS

CASE 1. A white male was first seen at the age of thirty-six. At that time he complained of a paroxysmal cough for which he had consulted numerous physicians. He had had various studies and therapeutic efforts such as tonsillectomy, adenoidectomy and sinus treatments, all without any effect. His examination at that time was entirely unproductive of results and a bronchogram showed no evidence of bronchiectasis.

The patient was lost sight of until some eight years later, at which time he returned with a complaint of severe paroxysmal pain in the left lower thoracic region with radiation to the precordium. His interval history revealed that after consulting numerous other physicians in regard to the cough he finally became discouraged and did nothing further. The cough gradually disappeared in the course of a few years.

In the past two years the pain just described had made its appearance. A typical attack was described as a sudden and unexpected onset of an excruciating pain beginning low in the left chest and spreading to the precordium but also occasionally up the back between the shoulders and down into the abdomen. The pain was so severe that the patient feared immediate death. However, the duration was not more than ten to twenty seconds and after the attack the patient felt entirely well. He developed an intense fear of these attacks. In the beginning they occurred at intervals of a few months but recently there had been one every two or three

weeks. The patient knew of no factor which would bring on or relieve the pain. The attacks occurred under all circumstances of rest and activity.

Physical examination of this patient revealed no abnormal findings whatever nor did the

pain was rarely more than fifteen or twenty minutes, and the attacks came at intervals of a few days to several weeks. Although the attacks did not last long, the patient had developed considerable fear and apprehension regarding them. He stated that with the onset of the pain

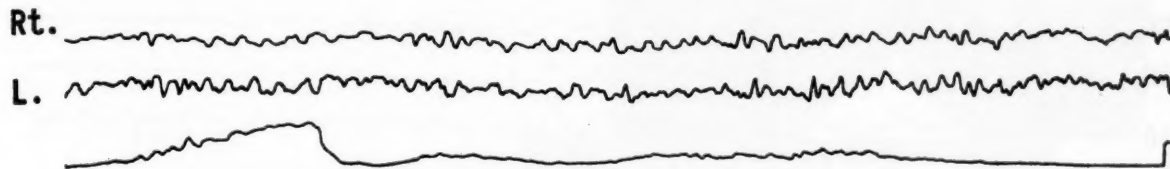


FIG. 1. Case I. Part of the electro-encephalographic tracing.

laboratory provide any further help. X-ray studies of the gallbladder and gastrointestinal tract were all non-productive. The electrocardiogram was normal at rest and after the exercise test. There were no abnormalities found in the cervical or thoracic spine.

In reviewing the history it was a temptation to assume that both the present complaint of paroxysmal pain and the cough of which he had formerly complained were due to a psychoneurosis. However, such a diagnosis would have been predicated upon exclusion since there were no definite findings to indicate that the patient had a psychoneurotic state. It was decided to have an electro-encephalographic study made. It was reported as follows: "All areas showed irregularity of the rhythm with prominent bursts of 6 to 7 per second waves. Alpha activity occurred to a moderate degree in the occipital regions, at a rate of 11 to 12 per second. Hyperventilation caused an increase of the 6-cycle waves. There was no spiking. The record was interpreted as showing a generalized dysrhythmia with paroxysmal 6 to 7 per second activity, suggestive of a convulsive state (psychomotor type)." A section of the tracing is shown in Figure 1. The patient was given phenobarbital, with complete relief of his symptoms. He has now been followed up for over a year and there have been no further attacks.

CASE II. This patient, a thirty-four year old man, presented himself with the complaint of severe, recurring paroxysms of pain in the right upper quadrant of the abdomen. These attacks of pain came on without any relationship to meals and began with a severe cramping just under the right costal margin. The pain frequently spread into the right chest and down into the lower abdomen. Nausea and vomiting sometimes were present. The duration of the

he felt a severe mental depression and had a feeling of hopelessness. He was as much concerned with these feelings as with the pain itself.

Nothing was found on physical examination. There were no abnormal neurologic findings. The accessory laboratory studies were all within normal limits as were x-ray studies of the gallbladder and the gastrointestinal tract. Perhaps the emotional disturbance in this individual provided the clue. An electro-encephalogram was made in another city and was reported to show changes typical of psychomotor epilepsy. At the last reports the patient had been doing well with use of sedatives and had had no attacks of pain in several months.

CASE III. This patient, a twenty-six year old man, presented himself because of peculiar attacks of substernal pain, rapid heart action, flushing and sweating. He had never had any serious illnesses and his family history was irrelevant. His first attack occurred while he was serving in the army in France. Although he had been through some very strenuous campaigns, at this time his unit was in a rest area and he felt that he was under no particular strain. The attack began while he was reading in his room. There was a severe substernal pain and shortly thereafter his pulse became rapid, he felt flushed and perspired freely. The pain was described as severe but not intense and the whole episode lasted only fifteen minutes. He was seen by a medical officer who sent him to the hospital where he had a thorough examination. It was not thought that this was an attack of paroxysmal tachycardia and since his examination in the hospital revealed no abnormalities he was returned to duty.

During the next six months he was released from the army and entered college. He had no other difficulties in this period of time. About

seven months from his first attack he had another one which occurred during the night and which awakened him. This was similar in every way to the first attack except that following this he was extremely depressed for the next two days. Since the first two attacks, he has had others at

there was no evidence of organic disease of the central nervous system in these patients, as has been pointed out the same symptoms might have occurred in the presence of a number of organic involvements. It was also fortunate that there were no

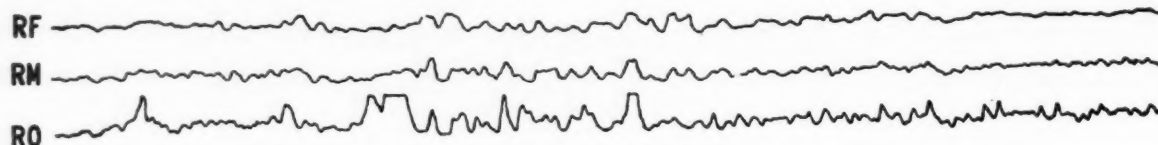


FIG. 2. Case III. Part of the electro-encephalographic tracing.

irregular intervals of from two weeks to three months. They have occurred during the daytime and also at night. The pattern has remained the same. There is first a severe substernal pain shortly followed by rapid heart action, flushing and sweating. The duration of the attack has never been longer than fifteen minutes.

Physical examination was entirely negative as were the accessory laboratory findings. X-ray studies of the gastrointestinal tract did not reveal any abnormalities and electrocardiogram was normal both before and after an exercise test. A careful psychiatric appraisal failed to reveal any information necessary for a diagnosis of a psychoneurosis. Therefore, it was decided to have an electro-encephalographic study made. This was reported as follows: "Both occipital regions showed a mixture of 16, 10, 8-9 and 7 per second waves, all decreased by light. The frontal and motor areas showed low voltage activity. On hyperventilation, random 5 to 6 per second waves appeared in all areas at one-half minute, and large 4 per second waves at two and one-half minutes. After cessation of hyperventilation, bursts of large, irregular 6 per second waves appeared in all areas for one minute. These findings were interpreted as those of a generalized dysrhythmia of non-specific nature, consistent with clinical epilepsy (although not diagnostic thereof)." A section of the tracing is shown in Figure 2.

The patient was given phenobarbital and up to this time has had no further attacks. Although he has been under observation for six months, it is still too early to be sure that no further attacks may occur due to the long period elapsing between the first and second episodes.

COMMENTS

These three cases are illustrative of the possibility that even severe pains may be the equivalent of epileptic disturbance. While

abnormalities of any sort found in the study of the gastrointestinal tract. The patients may have been saved an unnecessary operation by this fact. Finally, the question might arise as to whether the symptoms were not simply those of a psychoneurotic state which in itself might have been relieved by sedatives. None of these patients, however, showed any diagnostic signs of a psychoneurosis and furthermore the uniformity of the symptomatology together with the variation in time between attacks was very much against such a diagnosis.

CONCLUSIONS

Three cases of severe pain, apparently the equivalent of an epileptic seizure, are presented. The diagnosis was made partly by exclusion and partly by findings in the electro-encephalogram. Intense fear of the attacks was present in all three patients. They were relieved by treatment with sedatives. These cases suggest that electro-encephalographic studies may be of aid in the solution of difficult problems in the diagnosis of thoracic or abdominal symptoms.

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- Increased stool consistency
- Disappearance of gross blood and mucus
- Sigmoidoscopic evidence of mucosal healing follows symptomatic improvement

CRYMONASE

a specially processed
whole defatted duodenal substance



Clinically Effective in NON-SPECIFIC ULCERATIVE COLITIS

Clinical investigations, based on the hypothesis that non-specific ulcerative colitis is the result of a deficiency of an intrinsic factor normally present in the intestinal mucosa, showed effective response following the oral administration of defatted, desiccated duodenal mucosa.

CRYMONASE is a new specially processed duodenal substance whose chief action is the reduction of secretions of the gastro-intestinal tract and a decrease in motility. Special processing prevents autolysis of the substances normal to the raw tissues and they are retained in their natural state.

Supplied — Tablets: Bottles of 100, 250, 500, 1000;
Powder: 4-oz. bottle by weight. Literature on request.

Gill, A. M.: Proc. Roy. Soc. Med. 39:517, 1946.

IRWIN, NEISLER & CO.



DECATUR, ILLINOIS



Coming!

NOVEMBER 1949

SYMPOSIUM ON
DIABETES

Guest Editor

Russell Wilder, M. D.

MAYO CLINIC
ROCHESTER, MINN.



After twenty years
**MAXIMUM EFFICIENCY
 IN CONTRACEPTION**

Twenty years ago Lanteen Medical Laboratories began pioneer work in contraception, a field which was then widely denounced both within and outside of the medical profession. At that time, the most widely known contraceptive methods involved the use of such devices as lamb's wool tampons, rubber sponges and cotton plugs. Home-made vaginal suppositories were often prepared to be used either with these devices or alone. A greasy concoction of cocoa butter and boric acid, which was first heated in a skillet and then placed in the ice-box to cool, was in common use. Primitive as those methods seem today, they served a useful social and medical purpose.

The real pioneering task was to develop better products leading to more reliable and scientific contraceptive methods. Year after year Lanteen moved resolutely toward this goal, and, through continuous research and study, the Lanteen Diaphragm and Jelly method was developed.

With the years came gradual recognition. Many of those opposed to contraception came to see the rightness of the cause Lanteen had so steadfastly supported. The improved Lanteen Method was hailed as the answer to a difficult problem.

Now, after two decades of pioneering, Lanteen is still a leader in this field. The Lanteen Diaphragm and Lanteen Jelly are widely prescribed as a most modern, scientific advance in contraceptive technique.

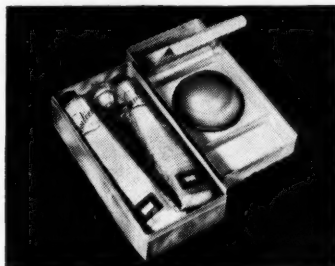
These twenty years have indeed been years of achievement.



The Lanteen Diaphragm and Lanteen Jelly are accepted by the Council on Physical Medicine and the Council on Pharmacy and Chemistry of the American Medical Association, respectively.

LANTEEN MEDICAL LABORATORIES, INC.

*Lanteen Jelly contains:
 Ricinoleic Acid 0.50%
 Hexylresorcinol 0.10%
 Chlorothymol 0.0077%
 Sodium Benzoate and
 Glycerine in a Traga-
 canth base.*



**900 North Franklin Street
 Chicago 10, Illinois**



a constant shield in allergy

In the treatment of allergy with antihistaminics it is essential to assure the patient a continuous, uniformly high degree of protection. Too rapid excretion or detoxification of the drug inevitably leads to a fluctuating, unreliable status, alternating between full protection and complete vulnerability. Chlorothen, Whittier, is distinguished pharmacologically by its prolonged action. Clinically, therefore, each dose may be relied upon to maintain a greater protective effect for a longer dosage interval—a constant defensive shield against allergens.

Whittier presents
long-acting



CHLOROTHEN

WHITTIER

Chlorothen, Whittier, has been proved by clinical trial to be highly effective in hay fever, vasomotor rhinitis, urticaria, angio-neurotic edema, and other allergic disorders. Side-reactions are usually mild and their incidence compares favorably with that of other antihistaminics.

To facilitate rapid solution and absorption, and hence prompt action, Chlorothen, Whittier, is issued as *uncoated* tablets of 25 mg. each for oral administration. One to two tablets every 4 to 6 hours, according to the response, is the customary dosage range.

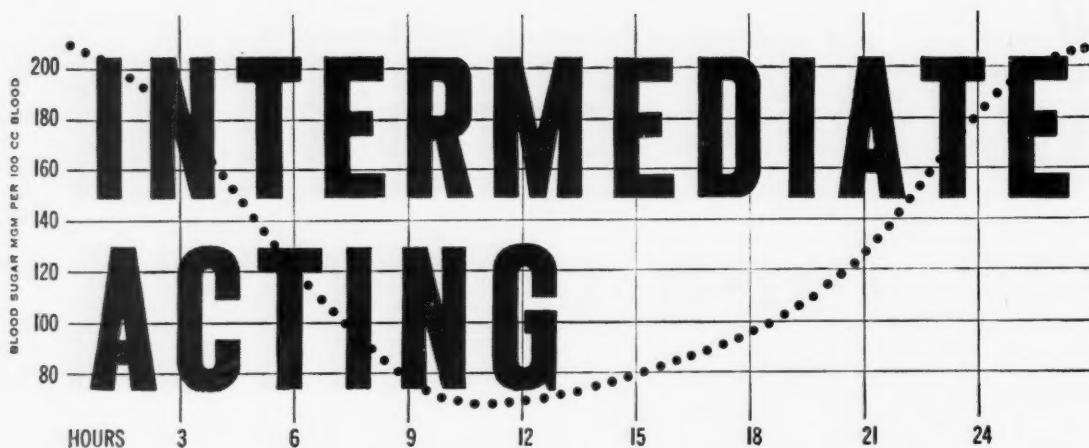
Packaged in bottles of 100 tablets.

Whittier
LABORATORIES

DIVISION NUTRITION RESEARCH LABORATORIES

CHICAGO 30, ILLINOIS





GLOBIN INSULIN

'B.W. & CO.'

*...was developed to fill the
"need for an insulin with
activity intermediate between
that of regular insulin and that
of protamine zinc insulin."¹*

IN 1939, Reiner, Searle and Lang described a new
"intermediate acting" insulin.

IN 1943, after successful clinical testing, the new sub-
stance was released to the profession as 'Wellcome'
brand Globin Insulin with Zinc 'B.W. & Co.'

TODAY, according to Rohr and Colwell, "Fully 80%
of all severe diabetics can be balanced satisfactorily"²
with Globin Insulin 'B.W. & Co.'—or with a 2:1 mixture
of regular insulin: protamine zinc insulin. *Ready-to-use*
Globin Insulin 'B.W. & Co.' provides the desired inter-
mediate action without preliminary mixing in vial or
syringe.

In 10 cc. vials, U-40 and U-80.

1. Rohr, J.H., and Colwell, A.R.: Arch. Int.
Med. 82:54, 1948.

2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.



'B.W. & CO. — a mark to remember



BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe 7, New York

The Story

History of Perandren® Reductions

January, 1939	10%
June, 1943	10%
January, 1947	20%
August, 1947	35%
February, 1949	up to 30%
June, 1949	up to 35%

*Ciba brand of testosterone
propionate, U. S. P.

Behind Perandren Price Reductions

AGAIN in June, Ciba reduced the prices of Perandren by amounts up to 35 per cent. This was the second such reduction in 1949.

Ciba introduced Perandren in 1936 as the result of the successful synthesis of testosterone propionate after years of exhaustive research. Ever since, this product has been subjected to a policy of investigation of all phases of its clinical application as well as the efficiency of its manufacture. This policy has been supported by large investments of money and research effort.

One result of this broad program has been the data and conservative advice which Ciba has been able to place at the disposal of the medical profession. Another result has been a gradual increase in manufacturing efficiency with its concomitant savings in cost. These savings, together with those which have come from the steadily increasing demand for Perandren, have been passed on in large part to the user, in conformity with what Ciba conceives to be its responsibility to the medical profession and the public.

Ciba was the first to bring about drastic reductions in the price of testosterone propionate. Now Perandren is benefiting many times the original number of patients, and, with the announcement of another price reduction, Perandren is less than 20% of its original price.

This is concrete evidence of our adherence to the Ciba policy of sharing economies from technological advances with those who enjoy the therapeutic benefits of Perandren, the Ciba brand of testosterone propionate.



JOSEPH S. BATES
President

Ciba

PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

PERANDREN—T. M. Reg. U. S. Pat. Off. 2/15/5000